A DESCRIPTIVE STUDY OF THE TEMPERATURE AT WHICH ANAESTHETIC REFRIGERATED DRUGS ARE STORED IN OPERATING THEATRE SUITES AT UNIVERSITAS ACADEMIC HOSPITAL

Submitted by Nadia Danielle Cloete in fulfilment of the requirements in respect of the Master's Degree MMed in the Department of Anaesthesiology in the Faculty of Health Sciences at the University of the Free State.

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Supervisor: Dr PM Van Zyl

MB ChB, MMedSc. (Clinical Pharmacology); Ph.D. (Clinical Pharmacology)

Department of Pharmacology, University of the Free State, South Africa

Declaration of Authorship

I, Nadia Danielle Cloete with student number 2004008310, declare that the coursework Master's Degree mini-dissertation A DESCRIPTIVE STUDY OF THE TEMPERATURE AT WHICH ANAESTHETIC REFRIGERATED DRUGS ARE STORED IN OPERATING THEATRE SUITES AT UNIVERSITAS ACADEMIC HOSPITAL that I herewith submit in a publishable manuscript format for the Master's Degree qualification in Anaesthesiology at the University of the Free State is my independent work, and that I have not previously submitted it for qualification at another institution of higher education.

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Table of Contents

Title Page i

Declaration of Authorship ii

Acknowledgements iii

Abstract vi

Keywords viii

Glossary of Terms ix

List of Abbreviations x

List of Tables xi

List of Figures xiii

Chapter 1: Literature Review 1

Introduction 1

Anaesthesia history: Single agent anaesthesia to balanced anaesthesia 1

Anaesthesia guidelines for drug storage 2

Drug degradation due to incorrect temperature storage 2

Temperature sensitive drugs stored within the cold drug storage unit at Universitas Academic Hospital 3

Solution to storage of temperature sensitive medication in anaesthetic practice 11

Solution to storage of temperature sensitive medication in other scopes of medicine 12

The purpose of this study 13

Implementations of study results 15

Recommendations for further research 15

References 16

Chapter 2: Publishable Manuscript 19

Abstract 22

Introduction 24

Methodology 27

Results 30

Discussion 36

References 41

Appendices 43

A: Cold drug storage unit (Cooler Box and Eutectic Gel pack) 43

B: Drug Package Information Leaflet 44

C: Digital Thermometer 61

D: Supplementary Table 62

E: Supplementary Figure 63

F: Letter of approval from HSREC 64

G: Letter of approval from HSREC after minor amendments 65

H: Permission from Department of Health 66
I: Permission letter from the Head of Department of Anaesthesiology 67
J: Permission letter from Theatre Manager 68
K: Research Protocol approved by the HSREC 69
L: Data collection form 119
M: Instructions to the Authors 120
N: Summary report: TurnitIn Plagiarism Search Engine 122

Abstract

Background

Temperature sensitive anaesthetic drugs require storage within individual theatre suites in order to be easily accessible to the anaesthetist for immediate use. This easy accessibility of drugs poses a risk of drug degradation due to incorrect temperature storage range. The method of storing refrigerated anaesthetic drugs in theatre suites, within a cooler box with a frozen eutectic gel pack (referred to as a cold drug storage unit) is well recognised and practiced. Yet, this method is poorly supported by literature and ill-defined in practice guidelines.

The aim of this study is to determine whether refrigerated drugs in the operating theatre suites at Universitas Academic Hospital (UAH), during working weekdays, are stored according to the manufacturer's temperature storage recommendation.

Method

A descriptive observational study was done on the cold drug storage units in nine theatres suites at Universitas Academic Hospital, at six fixed time slots from 07:30 to 17:00, on five consecutive weekdays. The cold drug storage unit temperatures were measured and was assessed for adequacy of storage of refrigerated anaesthetic drugs according to the manufacturer's recommendation on the package leaflet. The factors that could influence the internal environment of the cooler box were investigated; theatre room temperature, storage method of drugs within the cold drug storage unit, number, size and placement of the gel packs, the number of ampoules/vials and the utilisation of the operating theatre.

Results

Five hundred and forty five temperature measurements were taken of which 268 were theatre room temperature with an accompanying 267 cold drug storage unit temperature measurements and ten main storage refrigerator temperature measurements. The cold drug storage unit temperature, for all theatres for the five days, was in the range of $4{,}3^0C$ – $23{,}8^0C$ with a median of $14{,}8^0C$. This method of drug storage was not conducive to store all temperature sensitive anaesthetic drugs (requiring storage at 2^0C – 8^0C) on 235 temperature measurement (88%with a 95% Confidence

Interval of 83,6% to 91,4%). The statistically significant factor (p <0,001) determining the cold drug storage unit temperature to fulfil the manufacturers recommendation to maintain temperatures below 8^0C was the number, size and placement of the eutectic gel packs within the cold drug storage unit. With the use of two eutectic gel packs, placed above and below the drugs within a Styrofoam® cooler box, a desired temperature range of 2^0C – 8^0C can be maintained for an average of 4 hours and 30 minutes, to a maximum time frame of 9 hours and 30 minutes, in a theatre suite with a maximum room temperature of $25,7^0$C.

Conclusion

The current method of storing temperature sensitive drugs, in operating theatre suites at Universitas Academic Hospital does not fulfil the temperature storage requirements as set out by the drug manufacturer's most of the time. This method of passive refrigeration should not be abandoned as this study highlights the potential to maintain temperature below 8^0C...This potential success demonstrated in the study can be utilised to further research in determining the optimal storage conditions to store temperature sensitive anaesthetic drugs in an operating theatre suite within a resource limited environment.

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Keywords

Secure anaesthetic drug storage

Temperature sensitive medication storage

Anaesthetic drugs for balanced anaesthesia

Anaesthetic drug stability

Drug degradation products

Cold chain medicines

Drug manufacturer’s storage recommendations

Passive refrigeration

Cold drug storage unit

Cooler Box with a eutectic gel pack

Serial temperature measurements

Glossary of Terms

Cold drug storage unit

This is a temporary cold storage unit consisting of a Styrofoam® cooler box. Inside the box is a frozen eutectic gel pack and placed on top of this gel pack are the refrigerator drugs, packaged in plastic container with a lid, in its original carton or loosely inserted. (Appendix A)

Refrigerator drugs

Medications, which according to the manufacturers' recommendations, should be stored at 2^0C to 8^0C.

Room temperature

Comfortable temperature range indoors, considered to be 20^0C to 25^0C.

Stability

Capacity of a particular formulation, in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic, toxicological, protective and informational specifications. The extent to which a product remains, within specified limits, and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of manufacture.[1]

Degradation products

Degradation products are impurities resulting from chemical changes that can occur during drug manufacturing, storage and transportation in response to changes in light, temperature, pH and humidity. The presence of these can affect pharmaceutical safety.[2]

Theatre suite

An individual operating theatre within the main theatre complex at Universitas Academic Hospital.

List of Abbreviations

UAH	: Universitas Academic Hospital
HSREC	: Health Sciences Research Ethics Committee
DOH	: Department of Health
WHO	: World Health Organisation

List of Tables

List of Tables in Chapter 1: Literature Research

1. Succinylcholine Chloride package insert information and additional temperature storage recommendations by published studies.
2. Rocuronium package insert information and additional temperature storage recommendations by published studies.
3. Atracurium package insert information and additional temperature storage recommendations by published studies.
4. Cis - Atracurium package insert information and additional temperature storage recommendations by published studies.
5. Phenylephrine package insert information and additional temperature storage recommendations by published studies.
6. Heparin package insert information and additional temperature storage recommendations by published studies.
7. Oxytocin package insert information and additional temperature storage recommendations by published studies.
8. Syntometrine package insert information and additional temperature storage recommendations by published studies.
9. Insulin package insert information and additional temperature storage recommendations by published studies.
10. World Health Organisation recommendation for out of refrigerator vaccine storage

List of Tables in the Publishable Manuscript

I. List of commonly used drugs and recommended storage temperatures

II. Comparison of factors contributing to cold drug storage unit having a temperature below 8^0C and more than 8^0C

List of Figures

List of figures in Publishable Manuscript

1. Cold drug storage unit

2. Drugs placed within a plastic container in the cold drug storage unit

3. Digital thermometer probe placed within the plastic container containing the drugs

4. The temperature range of the cold drug storage unit summarised per theatre for the five days of data collection

5. The number of temperature measurements within a temperature range of 2^0C – 8^0C, temperature within manufacturer's recommendation compared to the number of measurements that were not within the manufacturer's recommendation

6. The temperature range of the theatre room temperature summarised per theatre for the five days of data collection

7. The storage method of placing drugs within the cold drug storage unit

8. The number of eutectic gel packs use, the size of the gel pack, and the placement of the eutectic gel pack(s) at the base or both on top and at the base of the drugs within the Styrofoam®

9. The median number of ampoules/ vials stored in cold drug storage unit per day and absolute number of ampoules/vials used per day per theatre

10. Greatest positive and negative fluctuation, amongst two consecutive temperature readings in the cold drug storage units for all theatres per day

Chapter 1: Literature Review

Critical and Synthesized Research of Literature

Introduction

A subset of drugs essential for anaesthesia practice are temperature sensitive and require storage in a temperature regulated environment. This environment, adhering to the manufacturer's recommended storage temperature, is essential to ensure reliable pharmacologic action. In a resource-limited setting these drugs are stored within a non-temperature regulated cooler box containing a frozen gel pack or packs in individual operating theatre suites during the time when the theatre is in use. This well-practised method of storage of refrigerated drugs in theatre suites has not been verified by published studies that actually measured the temperature in these storage units within real-life settings and assessed whether it adheres to the manufacturer's temperature storage recommendations.

Anaesthesia history: Single agent anaesthesia to balanced anaesthesia

The concept of modern anaesthesia originated in Massachusetts General Hospital in the United States of America on 16th October 1846 when WTG Morton demonstrated the use of a single agent anaesthesia, ether, to induce a sleep like state.[3] This form of anaesthesia was refined with the introduction of "balanced anaesthesia", consisting of premedication, inhalational anaesthesia and the use of muscle relaxants. In modern anaesthesia practice the pillars and conventional goals of general anaesthesia are autonomic nervous system control, unconsciousness, amnesia and immobility.[4] These goals are achieved with a range of anaesthetic agents, as oppose to a single agent, as previously practiced.. Each of these agents require secure storage according to set guidelines and recommendations to ensure safe drug delivery to the patient.[5]

Anaesthesia guidelines for drug storage

South African Society of Anaesthesia (SASA) in their Practice Guidelines of 2018 do not have prescribed recommendations for the storage of refrigerator drugs within individual theatre suites.[6]

The Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) have set out guidelines on best practice regarding the storage of drugs in Anaesthetic rooms.[5] These guidelines reiterate the importance of secure drug storage, the contribution it makes to patient safety and the recognition that even short delays in accessing drugs may result in adverse patient outcomes.

The Australian and New Zealand College of Anaesthetists share this sentiment and have specified, amongst other drugs, the need for muscle relaxants (which require storage at $2^0C - 8^0C$) to be immediately available in any setting where anaesthesia is administered.[7]

As a result of the above guideline requirements a standard of practice exists that allows for anaesthetic drugs to be stored within a cooler box in theatre suites to be within easy access to the anaesthetist when providing anaesthesia (Appendix A). This is a well-recognised and widely practised method of non-temperature regulated drug storage within theatre suites but is poorly supported by an existing body of literature.

Unfortunately these guidelines do not specify the manner or storage method that should be employed to store refrigerated drugs in individual theatre suites (without a refrigerator) during theatre lists.

Drug degradation due to incorrect temperature storage

Manufacturers determine the adequate temperature storage conditions for pharmaceutical products needed to maintain the efficacy and safety until the expiration date. These conditions are based on results from stability testing under a range of temperatures and therefore it is important that storage conditions be in compliance with package labelling information to prevent their degradation.[8]

The degradation of drugs are caused by chemical reactions (e.g. hydrolysis due to water exposure, oxidation due to oxygen exposure) and physical reactions (e.g. alteration of particle size,

disintegration of a suspension, absorption of water). Temperature is recognised as the most important factor driving these reactions and therefore if drugs are stored at conditions that exceed the recommended temperature it can lead to degradation and loss of potency.[9, 10]

It is important to note that it is not only storage of drugs above recommended temperatures that is a risk factor for accelerated degradation and risk of failure or unpredictable therapeutic response but that storage in temperatures below manufacturers' recommendation may lead to the denaturing of proteinaceous products. This poses a challenge in emergency situations requiring immediate drug administration by the anaesthetist.[10]

Our cold drug storage units in theatre suites are not temperature regulated and one can question whether these storage conditions are compliant with the manufacturers' storage recommendations to ensure the stability of the pharmaceutical products they contain.

Temperature sensitive drugs stored within the cold drug storage unit at Universitas Academic Hospital

Summarised in the tables below is a list of commonly stored drugs in the cold drug storage units in theatre suites at Universitas Academic Hospital.

Although the manufacturers of the individual drugs have a recommended temperature range for storage of these temperature sensitive drugs (Appendix B), it is noted that various studies have made additional recommendations to extend the prescribed temperature range. These studies, summarised below, use either clinical endpoints for potency of drugs or various assays measuring drug degradation products, to determine the extended temperature range storage and shelf life.

Table 1: Succinylcholine chloride (Suxamethonium®) package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Muscle relaxant
Concentration	50 mg/ml (2ml ampoule)
Manufacturer / Distributor	Fresenius Kabi, Bodene (Pty) Ltd
Manufacturer Recommended Storage Temperature	$2^0C – 8\ ^OC$

Additional Manufacturer Instructions	Protect from light
Recommendation by other studies	**Room temperature (light resistant) for 2,8 months.**[9] The aim of a study by De Winter et al. was to determine the content of five critically important drugs after being stored at the recommended refrigerated temperature (2^0C – 8^0C), room temperature (20^0C – 25^0C) and in an emergency transport vehicle (variable ambient temperature due to climate zone and season) at various intervals up to 12 months. The samples were analysed with liquid chromatography assay to determine drug stability. De Winter et al. concluded that succinylcholine chloride was stable for 2, 8 months at room temperature and only 1 month in an emergency physician transport vehicle due to factors such as sunlight, vibration and extremes of temperature. **Room temperature for 4,8 months**.[11] The aim of a study by Adnet et al. was to evaluate the effect of storage temperature on the stability of succinylcholine chloride solutions 20 mg/ml and 50mg/ml. Nuclear magnetic resonance spectroscopy was used to analyse the molecular composition. When assessing the monthly degradation rate for 50 mg/ml at 4^0C it was 0.3% compared to 8,1% at 37^0C. Adnet et al. concluded that when taking a loss of 10% potency as acceptable then the 20 mg/ml can be stored in emergency trolley carts at room temperature for 8,3 months and the 50 mg/ml can be stored under the same conditions for 4,8 months only.

Table 2: Rocuronium package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Muscle relaxant

Concentration	10 mg/ml (5ml ampoule)
Manufacturer / Distributor	Biotech Laboratories (PTY) LTD.
Manufacturer Recommended Storage Temperature	$2^0C – 8^0C$
Additional Manufacturer Instructions	Protect from light. Do not freeze. Keep vial in outer carton until use required. Use immediately after first opening.
Recommendation by other studies	**Rocuronium stored at room temperature for 14 days can be expected to result in unfavourable intubating conditions.**[12] The aim of this study by Kim et al. was to determine whether the storage temperature of rocuronium could have an influence on the pharmacodynamics of the rocuronium. 50 patients received rocuronium (0,45 mg/kg) stored in the refrigerator and 50 patients received rocuronium (0,45 mg/kg) stored at room temperature for 14 days ($20^0 – 29^0C$; median $25,1^0C$). Each group received a standard induction regimen and intubation was performed at 90 seconds after rocuronium administration with a 0,1 Hz single twitch applied. The intubation conditions were evaluated as excellent, good, poor and impossible. Kim et al. concluded that a statistically significant difference in intubating conditions occurred at 90 seconds between the two groups with the rocuronium stored at room temperature for 14 days resulting in unfavourable intubating conditions, namely a shortened clinical duration and prolonged time to twitch depression.

Table 3: Atracurium package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Muscle relaxant
Concentration	10 mg/ml (2.5 ml ampoule)
Manufacturer / Distributor	GlaxoSmithKline
Manufacturer Recommended Storage Temperature	2^0C – 8 ^{0}C
Additional Manufacturer Instructions	Protect from light Do not freeze
Recommendation by other studies	**Atracurium stored at room temperature for two weeks does not cause clinical significant degradation.**[13] The aim of this study by Frasca et al. was to compare muscle relaxation when atracurium stored at recommended refrigerated temperature (2^0C – 8^0C) and operating room temperature (15^0C – 20 ^{0}C) for 6 to 15 days were used. Patients were randomised into these two groups, received 0,5 mg/kg actual body weight of atracurium and muscle relaxation was assessed by neuromuscular transmission, train of four, vocal cord opening and Cormack grades. Frasca et al. concluded that when atracurium was exposed to room temperature for up to two weeks, this exposure did not cause enough degradation to be clinically significant.

Table 4: Cis – Atracurium package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Muscle relaxant
Concentration	2 mg/ml (2.5ml ampoule)
Manufacturer / Distributor	GlaxoSmithKline

Manufacturer Recommended Storage Temperature	$2^0C – 8^0C$
Additional Manufacturer Instructions	Protect from light Do not freeze Do not remove from outer carton till administration Diluted solution can be stored at $5^0C – 25^0C$
Recommendation by other studies	**Room temperature (light resistant) for 3,8 months**.[9] The aim of this study by De Winter et al. was to determine the content of five critically important drugs after being stored at the recommended refrigerated temperature ($2^0C – 8^0C$), room temperature ($20^0C – 25^0C$) and in an emergency transport vehicle (variable ambient temperature due to climate zone and season) at various intervals up to 12 months. The samples were analysed with liquid chromatography assay to determine drug stability. De Winter et al. concluded that cis-atracurium was stable for 3,8 months at room temperature and 4,7 months in an emergency physician transport vehicle.

Table 5: Phenylephrine hydrochloride package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Vasopressor
Concentration	10 mg/ml (1 ml ampoule) 100 mg/ml (0,5 ml ampoule, 10% solution)
Manufacturer / Distributor	Biomedi, S.A. Abbott (10 mg/ml) Soflens (PTY) Ltd (10% solution)
Manufacturer Recommended Storage Temperature	Store at or below 25^0C (10 mg/ml) $2^0C – 8^0C$ (10% solution)
Additional Manufacturer Instructions	Protect from light Keep covered in carton till use
Recommendation by other studies	**The National Center for Biotechnology Information recommends that when phenylephrine is diluted in**

	5% dextrose it will be stable for 48 hours at a pH of 3,5 – 7,5.[14] It cautions against prolonged exposure of phenylephrine to air or strong light as it may cause oxidation and discolouration.[14] **Phenylephrine when diluted in 0, 9% sodium chloride and stored at room temperature is physically and chemically stable for 60 days.**[15] In this study by Jansen et al. the physical and chemical stability of phenylephrine, once diluted in polyvinyl chloride bags were evaluated. The stability was measured by high performance liquid chromatography over a period of 60 days. Jansen et al. concluded that when phenylephrine hydrochloride was diluted to 200 ug/ml and 400 ug/ml with 0, 9% sodium chloride, stored at room temperature with fluorescent lighting over a period of 60 days that it was both physically as well as chemically stable with less than 5% degradation.

Table 6: Heparin package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Anticoagulant
Concentration	1000 U/ml, 5000 U/ml (4ml ampoule)
Manufacturer / Distributor	Fresenius Kabi
Manufacturer Recommended Storage Temperature	Below 25^0C
Additional Manufacturer Instructions	Do not freeze

No recommendations by other studies were found.

Table 7: Oxytocin package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Oxytocic
Concentration	10 IU/ml (1 ml ampoule)
Manufacturer / Distributor	Specpharm
Manufacturer Recommended Storage Temperature	$2^0C – 8^0C$
Additional Manufacturer Instructions	Do not freeze Do not remove ampoule from carton until use Protect from direct sunlight
Recommendation by other studies	**-5^0C to -20^0C up to 7 days.**[14] In this study by Nassata et al. oxytocin ampoules were stored at temperatures -5^0C and -20^0C for 7 days with a control stored at 4^0C. After five freeze-thaw cycles the amount of oxytocin was determined by liquid chromatography triple quadrupole mass spectrometry assay. Nassata et al. concluded that no significant difference in change in concentration was found between the groups and the control.

Table 8: Syntometrine® package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Oxytocic Ergometrine maleate and oxytocin
Concentration	Syntometrine® 500 micrograms/ml and oxytocin 5 IU/ml (1ml ampoule)
Manufacturer / Distributor	Adcock Ingram Critical Care (Pty) Ltd
Manufacturer Recommended Storage Temperature	$2^0C – 8^0C$
Additional Manufacturer Instructions	Do not freeze. Protect from light.

	Do not remove from the outer container until required for use
Recommendation by other studies	**World Health Organisation's Essential Medicine and Health Products guideline states that when ampoules of Syntometrine® are left at room temperature, exposed to light, the level of active ingredient reduces by 21% – 27% per month.** [17] If no refrigerator is available the World Health Organisation regards storage of Syntometrine®, at room temperature to a maximum of 30^0C, for a maximum of 3 months as acceptable. [17]

Table 9: Insulin package insert information and additional temperature storage recommendations by published studies.

Pharmacological classification	Hypoglycaemic agent
Concentration	100 U/ml (10ml vial)
Manufacturer / Distributor	Novo Nordisk A/S
Manufacturer Recommended Storage Temperature	2^0C – 8^0C Room temperature (maximum 25^0C) for one month
Additional Manufacturer Instructions	Do not freeze Keep out of sunlight
Recommendation by other studies	**If no refrigerator is available then insulin can be stored at room temperature for up to 2 weeks.** [18] The aim of this study by Vimalavathini et al. was to determine how improper temperature storage affects the potency of insulin . Two insulin formulations were stored at five different temperatures and potency tested by liquid chromatography every 7 days for 28 days. On the 25^{th} day insulin tolerance test was performed on rabbits. When insulin was stored at 32^0C and 37^0C there was a 14% – 18% decrease in potency but no significant decrease in

	blood glucose level when the insulin tolerance test was performed. Vimalavathini et al. therefore showed that insulin can be stored safely at room temperature for a maximum of two weeks.

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This data summarises the manufacturers' storage temperature recommendations. If a passive refrigerator system (i.e. cold drug storage unit) maintains a storage temperature range of $2^0C - 8^0C$ all the temperature sensitive drugs will adhere to the manufacturers' recommendations when stored in these units. It has been demonstrated by additional studies conducted that indicate optimal drug pharmacokinetics or pharmacodynamics when the drugs are stored in temperatures outside the manufacturer's recommended temperature range. These can merely be viewed as hypotheses and therefore have not been incorporated by the manufacturer to include it within their recommendations. It can be concluded that in a theatre suite, within a resource limited environment, the ideal cold drug storage unit should maintain an internal temperature of $2^0C - 8^0C$ in order to store all temperature sensitive anaesthetic drugs.

Solution to storage of temperature sensitive medication in anaesthetic practice

The current standard of practice at Universitas Academic Hospital regarding the handling of refrigerator drugs and maintaining adequate storage are as follows. At 07:00 the anaesthetic nurse of a particular theatre suite collects the refrigerator drugs from a refrigerator where drugs are stored at 4^0C to 6^0C in the theatre medication stock room. The anaesthetic nurse places the drugs in a Styrofoam® cooler box with eutectic gel pack/s which can be seen as the "annexe" to the controlled storage refrigerator (Appendix A).

Styrofoam® is a plastic polystyrene, a non-metallic solid with low thermal conductivity making it a good thermal insulator.[20] The iced gel pack decreases the Styrofoam® cooler box's interior temperature and the insulation property of the Stryrofoam® limits the heat that enters the cooler box. The manner of placement of the drugs within this Styrofoam® cooler box is not standardised — it is either placed in a plastic container, in the original carton or loosely placed. This cold drug storage unit is placed on the anaesthetic drug trolley in each theatre suite and subsequently exposed

to ambient theatre temperatures. The current practice requires return of drugs to the controlled temperature unit (refrigerator) to the theatre medication stock room at the end of the theatre list and permits reuse if the medication if unopened. The duration of use of a particular theatre determines the time that the drugs are out of a controlled temperature environment; on average 3 hours to 10 hours per day.

The lack of "annexe" temperature display, regulation and monitoring pose the risk for drugs being exposed to temperatures deviating from the manufacturers' recommendations. Currently it is unclear what the temperature is that the drugs are stored at in these cold drug storage units. It is unclear whether the room temperature, storage method of drugs within cold drug storage unit, the number and size of ice pack usage and the number of ampoules affect the temperature within the cold drug storage unit to a significant extent or not.

Solution to storage of temperature sensitive medication in other scopes of medicine

The challenge of maintaining drugs at the recommended temperature range is not unique to anaesthetic practice but is also encountered by critical care transport teams and in the maintenance of a vaccine cold chain during off-site immunisation outreach.

Critical care transport teams transport temperature sensitive medication (e.g., succinylcholine and rocuronium) in environments that potentially exceed the manufacturers' recommended temperature threshold. The strategies that have been employed to optimise temperature control for storage of these drugs in critical care transport include high technology coolers, small portable refrigerators and placement within a PackIt Cooler Box.[10] The latter method is similar to our current practice in theatre suites at Universitas Hospital. When the effectiveness of this medication storage strategy was tested in the critical care transport industry by conducting a simple trial it was concluded that this industry accepted strategy was not able to maintain the drugs at manufacturers' recommended temperature for trip durations lasting longer than 3 hours.[10]

During the transport of immunisations the cold chain; a system needed to ensure storage of vaccines in temperature regulated conditions, is critical to ensure the required potency of these sensitive biological products.[21]

The World Health Organisation (WHO) recommends the storage of these vaccines in various storage units for transport, short term usage when no electricity is available or the refrigerator is not in working condition.[21] The methods recommended by WHO are summarised in the table below.

Table 12: WHO recommendation for out-of-refrigerator vaccine storage

Name of Unit	Description	Cold life (Temperature < 10^0C)
Cold Boxes	Insulated container lined with frozen ice packs	Two to seven days at room temperature of up to 43^0C
Vaccine Carriers	Small insulated containers with frozen ice packs	18 to 50 hours at room temperature of up to 43^0C
Adjuncts		
Water-packs	Leak proof, flat plastic containers filled with tap water. Lines the inside of cold boxes or vaccine carriers. Correct size and number of water packs to be used is instructed on the inside of lid container.	
Foam pads	Sponge like, soft material placed on top of water packs inside a vaccine carrier allowing full closure of carrier lid.	

The purpose of this study

In daily anaesthetic practice it is essential for drugs to be easily accessible to the anaesthetist — this is achieved by the storage of temperature sensitive drugs placed within a non-temperature regulated cooler box in a theatre suite. If this environment is not within the manufacturers' recommended temperature storage range this could lead to the degradation of drugs, loss of potency and adverse patient outcome. [10, 19]

When searching for literature to support our daily practice it was noted that no publication to date exists to define the various methods employed in individual theatre suites to store refrigerator

anaesthetic drugs and the effectiveness of such methods to maintain an adequate manufacturer recommended temperature throughout the operating day.

This led to the following research question: Are we storing refrigerated anaesthetic drugs in operating theatre suites at Universitas Academic Hospital according to the drug manufacturers' temperature recommendations?

The aim of this descriptive observational study was to assess whether the current temperature storage of refrigerator drugs in operating theatre suites during the work day week are compliant with the manufacturers' temperature storage recommendations.

The primary outcome of this study was to measure the temperature in the cold drug storage units used in theatre suites during daytime working hours and to compare this to the manufacturers' storage temperature recommendations stated on the package information leaflets (Appendix B). This outcome was achieved by placing a digital thermometer (Appendix C) within the plastic container housing the drugs within the cooler box. This thermometer has a temperature measuring range of -20^0C to 70^0C and the manufacturer's assurance of an accuracy of $\pm 1^0$C. The temperature measurements were taken of the cold drug storage units placed in nine theatre suites at Universitas Academic Hospital over 5 consecutive workdays on six fixed time slots from 07h30 to 17h00.

The temperatures measured in the cold drug storage unit were directly compared to with the manufacturers' temperature recommendations. These comparisons allowed us to assess the effectiveness of the current storage method for ensuring optimal storage of temperature sensitive anaesthetic drugs in theatre operating suites.

A secondary outcome was to assess whether additional variables; room temperature, storage method of drugs, eutectic ice pack usage, number of ampoules and theatre suite usage had any relationship with the measured temperatures within the cold drug storage unit. This outcome was achieved by measuring the room temperature on each occasion when the temperature reading of the cold drug storage unit was measured, noting the way the drugs were stored within the cod drug storage unit, noting the size, amount and placement of the eutectic ice packs used, counting the ampoules/vial within the cold drug storage unit and noting the time that the theatre suite (in which a cold drug storage unit was located in) was used for a particular day.

An analysis was performed between the groups in which the cold drug storage unit was adequate to store all the temperature sensitive medication and the group in which the cold drug storage units

were inadequate to store temperature sensitive drugs. The variables contributing to the cold drug storage units' maintenance of manufacturer's temperature recommendation range were identified.

An additional secondary outcome was to assess whether the aforementioned variables had any relationship with the changes in cold drug storage unit temperature. This outcome was achieved by analysing the data collected of the cold drug storage unit with the greatest increase in temperature and the greatest decrease in temperature fluctuation between two consecutive temperature measurements per day.

With this information a recommendation can be made to improve the cold drug storage unit's maintenance of temperature within operating theatre suites.

Implementations of study results

The knowledge gained from this study can be implemented in daily anaesthetic practice in the following manner: educating the anaesthetic personnel on the storage method of refrigerator drugs that allow a temperature range recommended by the manufacturer and minimising the number of ampoules/ vials placed in the cold drug storage unit therefore exposing less drugs to temperature fluctuations.

This study can contribute to further research to provide a recommended standard of practice by guidelines for the storage of refrigerator drugs outside of a refrigerator for a period of time in an anaesthetic practice or can be used as motivation to substantiate the need for permanent mini drug storage refrigerators in each operating theatre suite.

Recommendations for further research

Further research is needed regarding the actual degradation of anaesthetic drugs due to incorrect temperature storage conditions in operating theatre suites and the exposure to daily fluctuations of temperature caused by daily cycling between the main storage refrigerator and theatre operating suites. The clinical significance of such degradation also requires investigation.

Chapter 1 word count without references: 3940

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Chapter 2: Publishable Manuscript

Title:

A DESCRIPTIVE STUDY OF THE TEMPERATURE AT WHICH ANAESTHETIC REFRIGERATED DRUGS ARE STORED IN OPERATING THEATRE SUITES AT UNIVERSITAS ACADEMIC HOSPITAL.

Authors:

Cloete, ND

MBChB, DA (SA)

Department of Anaesthesiology, University of Free State, South Africa

Van Zyl, PM

MB ChB, MMedSc .(Clinical Pharmacology); Ph.D. (Clinical Pharmacology)

Department of Pharmacology, University of the Free State, South Africa

Van Rooyen, C

Department of Biostatistics, University of the Free State, South Africa

Correspondence:

Dr Nadia Danielle Cloete

35 Elizabeth Eybers, Langenhovenpark, Bloemfontein, 9330

nadiagantana@gmail.com

+27 82 483 3637

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Professor BJS. Diedericks – my mentor

Dr E. Turton – the Head of Department of Anaesthesiology

The lifelong support of Xavier Cloete, and cheering-on spirit of India and Taig Cloete, were the driving force for my ability to complete this work.

Conflict of interest

I declare that I have no financial or personal relationships which may have inappropriately influenced me in writing this paper.

Abstract

Background

Temperature sensitive anaesthetic drugs require storage within individual theatre suites in order to be easily accessible to the anaesthetist for immediate use. This easy accessibility of drugs poses a risk of drug degradation due to incorrect temperature storage range. The method of storing refrigerated anaesthetic drugs in theatre suites, within a cooler box with a frozen eutectic gel pack (referred to as a cold drug storage unit) is well recognised and practiced. Yet this method is poorly supported by literature and ill-defined in practice guidelines. The aim of this study is to determine whether refrigerated drugs in the operating theatre suites at Universitas Academic Hospital (UAH), during working weekdays, are stored according to the manufacturer's temperature storage recommendation.

Method

A descriptive observational study was done on the cold drug storage units in nine theatres suites at Universitas Academic Hospital, at six fixed time slots from 07:30 to 17:00, on five consecutive weekdays. The cold drug storage unit temperatures were measured and was assessed for adequacy of storage of refrigerated anaesthetic drugs according to the manufacturer's recommendation on the package leaflet. The factors that could influence the internal environment of the cooler box were investigated; theatre room temperature, storage method of drugs within the cold drug storage unit, number, size and placement of the gel packs, the number of ampoules/vials and the of utilisation of the operating theatre.

Results

Five hundred and forty five temperature measurements were taken of which 268 were theatre room temperature measurements with an accompanying 267 cold drug storage unit temperature measurements and ten main storage refrigerator temperature measurements. The cold drug storage unit temperature for all theatres for the five days was in the range of $4{,}3^0C$ – $23{,}8^0C$ with a median of $14{,}8^0C$. This method of drug storage was not effective to ensure optimal storage temperature for all temperature-sensitive anaesthetic drugs (requiring storage at 2^0C – 8^0C) on 235 temperature measurements (88% with a 95% Confidence Interval of 83,6% to 91,4%). The number and placement of the of the eutectic gel packs within the cold storage units was a statistically significant factor ($p < 0{,}001$) determining

the cold drug storage unit temperature to fulfil the manufacturers' recommendation to maintain temperatures below 8^0C .

Conclusion

The current method of storing temperature sensitive drugs, in operating theatre suites at Universitas Academic Hospital does not fulfil the temperature storage requirements as set out by the drug manufacturer's most of the time. This method of passive refrigeration should not be abandoned as this study highlights the potential to maintain temperature below 8^0C. With the use of two eutectic gel packs, placed above and below the drugs within a Styrofoam® cooler box, a desired temperature range of $2^0C – 8^0C$ can be maintained for an average of 4 hours and 30 minutes, to a maximum time frame of 9 hours and 30 minutes, in a theatre suite with a maximum room temperature of $25,7^0C$.This potential success demonstrated in the study can be utilised to further research in determining the optimal storage conditions to store temperature sensitive anaesthetic drugs in an operating theatre suite within a resource limited environment.

Introduction

The drugs used in anaesthesia require storage according to manufacturer's recommendation to ensure reliable pharmacological action.[1] Incorrect storage conditions may result in accelerated degradation of drugs, loss of potency and adverse patient outcomes.[2] It is therefore imperative that drugs used in anaesthesia are stored securely while remaining easily accessible for anaesthetic use in daily practice.[2,3]

The conditions of storing refrigerated anaesthetic drugs during theatre operating hours in individual theatre suites are ill defined in South African Anaesthetic guidelines.[4] There is a lack of published literature on the effectiveness of the current cooler box units used in theatre suites to create optimal storage according to manufacturers' recommended temperature thresholds. A comprehensive list of drugs regularly contained within these cold drug storage units, the manufacturer's recommended storage temperature and the recommendations by published literature are shown in Table 1.

Table I: List of commonly used drugs and the recommended storage temperatures

Drug name	Brand name (Manufacturer)	Concentration	Manufacturer recommendation	Published literature recommendation
Succinylcholine chloride	Suxamethonium® (Fresenius Kabi, Bodene (Pty) Ltd)	100 mg / 2ml	$2^0C – 8^0C$	Room temperature for 4,8 months[5] , Room temperature (light resistant) for 2,8 months[6]
Rocuronium	Rocuronium (Biotech Laboratories (Pty) Ltd)	50 mg / 5ml	$2^0C – 8^0C$	Storage in room temperature for 14 days lead to unfavourable intubating conditions[7]
Atracurium	Atracurium (GlaxoSmithKline)	10 mg / ml	$2^0C – 8^0C$	Storage at room temperature for two weeks does not cause clinical significant drug degradation[8]
Cis – Atracurium	Nimbex® (GlaxoSmithKline)	5 mg / 2ml	$2^0C – 8^0C$ (Diluted solution can be stored at $5 – 25^0C$)	Room temperature (light resistant) for 3,8 months[6]
Phenylepherine hydrochloride	Phenylepherine® (Biomedi S.A., Abbott)	10 mg / ml	At or below 25^0C	If diluted in 0,9% sodium chloride and stored at room temperature it is physically and chemically stable for 60 days[9]. Can be diluted in 5% dextrose and will be stable for 48 hours at a pH of 3,5 – 7,513. [10]
Phenylepherine hydrochloride	Minims Phenylepherine® (Soflens(Pty) Ltd)	50 mg / 0,5ml	$2^0C – 8^0C$ (2,5% solution store below 25^0C)	
Heparin	Heparin (Fresenius Kabi)	1000 U / ml, 5000 U / ml	Below 25^0C	No recommendation by other studies
Oxytocin	Spec Oxytocin® (SpecPharm (Pty) Ltd)	10 U / ml	$2^0C – 8^0C$	Stored at -5^0C to -20^0C for 7 days (with five freeze thaw cycles) compared with storage at 4^0C showed no difference in change on concentration[11]
Ergometrine Maleate & Oxytocin	Syntometrine® (Adcock Ingram (Pty) Ltd)	5U Oxytocin & 0,5mg Ergometrine / ml	$2^0C – 8^0C$	Room temperature, exposed to light, the level of active ingredient reduces by 21 – 27% per month. Storage at room temperature to a maximum of 30^0C for a maximum of 3 months is acceptable[12]
Insulin	Actrapid HM® Novo Nordisk A/S	1000 U / 10ml	$2^0C – 8^0C$ (Room temperature for one month)	Room temperature at 12 weeks[13]

To maintain a cold chain and thereby ensure pharmaceutical stability, the refrigerated anaesthetic drugs are stored in a temperature regulated main storage fridge, prior and after a working theatre day. When removed from this temperature regulated environment, the drugs are placed within a cooler box (Styrofoam®) containing an eutectic gel pack (referred to as a "cold drug storage unit") and exposed to environmental temperature for the duration of the working theatre day.

Figure 1: Cold drug storage unit

Temperature is recognised as the most consistent factor driving both the chemical and physical degradation of drugs.[6, 14] Inadequate storage of these anaesthetic drugs; whether not easily accessible for the anaesthetist or incorrect temperature storage, can result in delay of drug administration and unpredictable therapeutic response. This has the potential to compromise timely emergency patient treatment in an anaesthetic environment.[15]

The purpose of this study is to investigate whether the temperature storage conditions of anaesthetic refrigerated drugs in operating theatre suites at UAH are maintained according to the manufacturer's temperature recommendations during typical work days.

A descriptive observational study was done, measuring the temperatures that refrigerator drugs were exposed to when stored in cooler box units in operating suites. Storage temperatures were compared to the manufacturer's temperature recommendations for individual drug storage to determine whether the storage method adhered to adequate temperature storage requirements. Factors that could influence the internal environment of the cooler box were investigated; theatre room temperature, storage method of drugs within the cold drug storage unit, number, size and placement of the gel packs, the number of ampoules/vials and utilisation of the operating theatre.

Methodology

A descriptive observational study design was used in this study. The ethics clearance was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State in Bloemfontein, South Africa.

The study population consisted of the nine cold drug storage units containing the refrigerated drugs in nine theatre suites at UAH. Data was collected on 28th of October 2019 to the 1st of November 2019 (Monday to Friday) at six fixed time slots per day. An initial pilot study was performed, which highlighted the need for minor amendments to be made, resubmitted to the HSREC with approval granted.

The theatre suites included in this study were the nine theatre suites (Theatre 1 – 5 and 8 – 11) within the main theatre complex at UAH from 07h30 – 17h00. This study excluded cardiothoracic theatres within the main theatre complex due to the large fluctuation in the theatre room temperature required by the surgical procedure and all UAH Annex theatres due to logistical reasons.

The cold drug storage unit consisted of a Styrofoam® cooler box containing an eutectic gel pack at the base. The refrigerator drugs are placed on top of the gel pack within a plastic container; loosely or within their original packaging as illustrated in Figure 2. The packaging of the drugs and the position, size and number of eutectic gel packs were placed at the discretion of the anaesthetic nurse (as per standard daily practice).

Figure 2: Drugs placed within a plastic container in the cold drug storage unit

A digital thermometer, Lasec SA (Pty) Ltd stock code: H3THE006Z-000002, with a temperature measuring range of -20^{0}C to 70^{0}C and a manufacturer's assurance of an accuracy of ±1^{0}C was used. The thermometer has a digital display

(placed on the outside of the cold drug storage unit) and a 1.5 meter cord with the measuring probe that was placed in a standard position within the plastic drug container within the cooler box (as noted in Figure 3). A synchronization reading procedure was done on the day of the pilot study and the first day of data collection. (Synchronization reading procedure: personal communication with Professor W Rae, Previous Head of Department of Medical Physics at University of the Free State, South Africa). The participants in this study was not blinded to the temperature display of the cold drug storage unit.

Figure 3: Digital thermometer probe placed within the plastic container containing the drugs

At 07h00 the temperature measurement of the main drug storage refrigerator was taken and placement of two thermometers in nine theatres — one within the cold drug storage unit and one to measure ambient temperature.

The following procedure occurred at six time slots 07:30, 09:00, 11:00, 13:00, 15:00, and 17:00:

Temperature measurement: Ambient theatre and Cold Drug Storage Unit

Storage method of drugs within the cold drug storage unit was noted

Gel pack size, number and position within the cold drug storage unit

Number of ampoules/vials in the cold drug storage unit

Start and end of anaesthetic time for the theatre day in each theatre

At 17h30 the temperature reading of the main drug storage refrigerator, where the drugs in the cold drug storage unit was returned after 17h00, was noted.

The aim of this study was to assess whether the current temperature storage of refrigerator drugs in operating theatre suites at Universitas Academic Hospital during daytime working hours are compliant with the drug manufacturers' storage recommendations.

The primary objective in this study was to measure the temperature in the cold drug storage unit used in theatre suites for the storage of drugs during daytime working hours and to compare this to the manufacturers' storage temperature recommendations stated on the package information leaflets.

The secondary objective was to assess whether variables such as; theatre room temperature, the storage method of drugs within the unit, , the eutectic gel pack usage and the number of drug ampoules or vials in the cold drug storage unit and theatre utilisation held any relationship with the temperature measured within the cold drug storage unit.

An additional secondary outcome was to assess whether the aforementioned variables had any relationship with the fluctuations noted in cold drug storage unit temperature.

To minimise bias, the Hawthorne effect and the effect of confounders on the study results, the nursing staff were instructed not to change their practice in the packaging of the cold drug storage units. Observational bias was reduced by using standardized digital thermometers with accurate continuous display of temperature. The temperature display of the thermometer was visible to the nursing staff, anaesthetist and the data collector, Temperature readings might have been affected by the number of times the Styrofoam® cooler box and plastic container or carton was opened and whether the lid of either or both is placed securely when closed to prevent excessive influx of heat once anaesthetic drugs have been removed. These confounders however could not be accounted for in this study.

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Statistical Methods: Analysis of Data

Analysis of the data collected was performed by the Department of Biostatistics of the University of the Free State. Descriptive statistics namely maximum, minimum and median values were calculated for continuous data. Frequencies and percentages were calculated for categorical data. Fisher's exact test and Chi-square tests were used for non-parametric comparative data and a p value $< 0,05$ was used as the cut-off for statistical significance.

Results

Primary outcome results

A total of 565 temperature measurements were scheduled to occur in the data collection period but 20 (3,5%) could not be recorded due to the unavailability of the cold drug storage units for particular theatres. Therefore 545 temperature measurements were recorded in total, with 268 theatre room temperature measurements, 267 cold drug storage unit temperature measurements and ten main storage refrigerator temperature measurements.

The minimum, median and maximum cold drug storage units temperature (n = 267) for each theatre for the week is summarised in Figure 4. The overall combined cold drug storage unit temperature for the period of data collection was a minimum of 4,3^{0}C, maximum of 23,8^{0}C with a median temperature value of 14,8^{0}C.

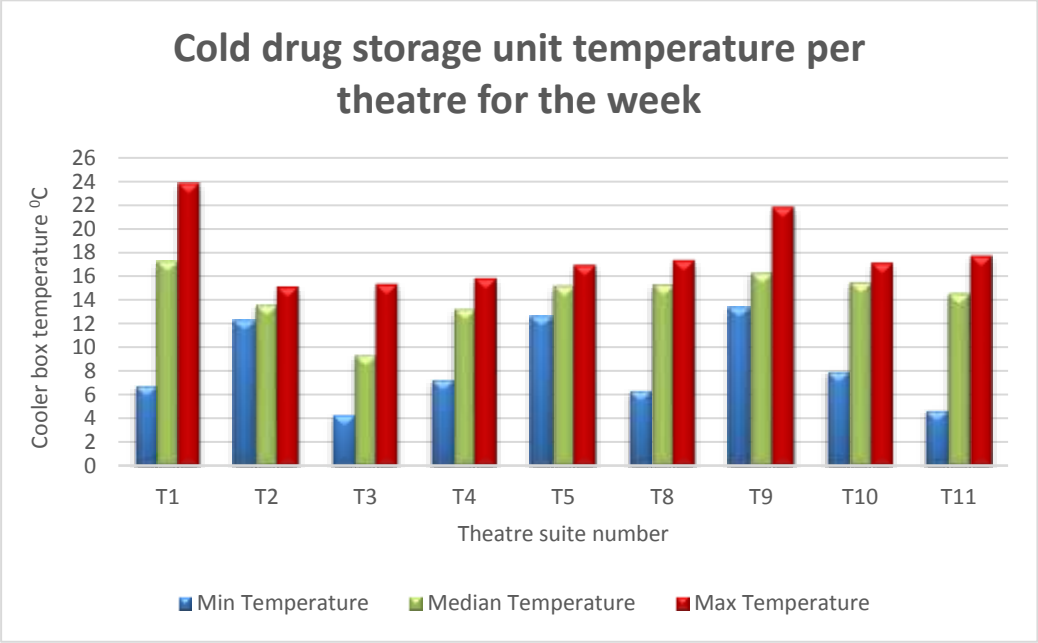

Figure 4: The temperature range of the cold drug storage unit summarised per theatre for the five days of data collection

In order for the all the temperature sensitive drugs to be stored within the cold drug storage unit according to manufacturers' recommendations, the temperature within the cold drug storage unit would have to be 2^{0}C – 8^{0}C. Figure 5 shows the proportion of readings that complied with the manufacturer's recommendations compared to the proportion that didn't.

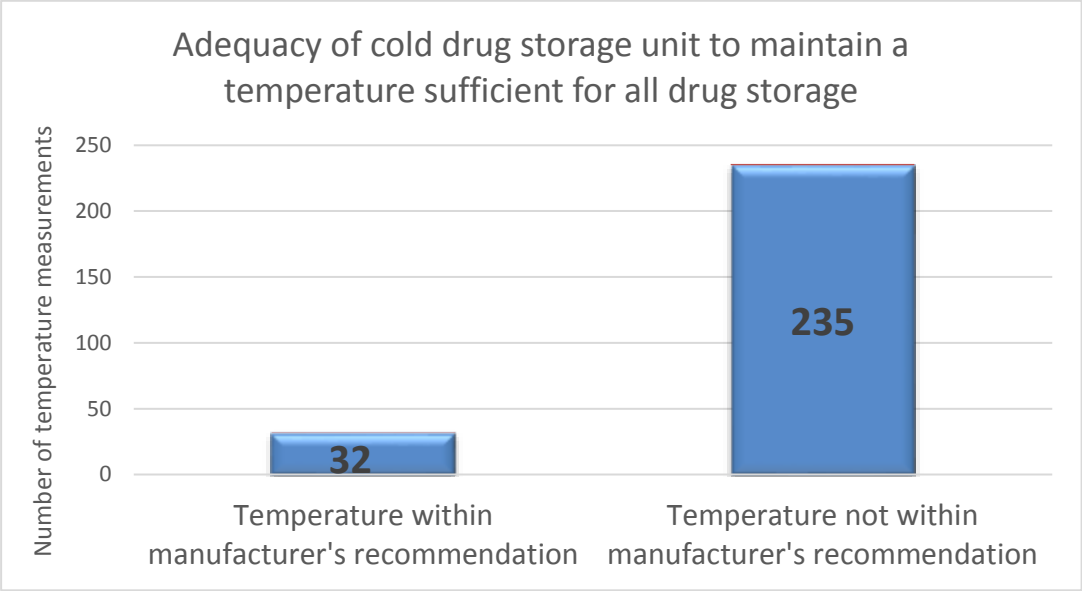

Figure 5: The number of temperature measurement within a temperature range of 2^0C – 8^0C, temperature within manufacturer's recommendation compared to the number of measurements that were not within the manufacturer's recommendation

Figure 5 illustrates that only 32 readings of the 267 cold drug storage temperature readings (12 % with a Confidence Interval of 8.65% to 16,4%) were conducive to store all the temperature sensitive anaesthetic drugs according to the manufacturer's recommendation. In this study this method was ineffective to store temperature sensitive drugs on 235 reading of 267 cold drug storage temperature readings (88% with a 95% Confidence Interval of 83,6% to 91,4%). When taking into consideration the limitation of the measuring instrument, the digital thermometer with an accuracy of ± 1^0C, the above temperature range of adequacy was extended to 1^0C – 9^0C (from 2^0C – 8^0C). With this limitation being accounted for the number of temperature measurements that were conducive to store all refrigerated anaesthetic drugs increased, with an additional 9 temperature measurement readings to a total of 41 (15,4%) adequate temperature measurements, within the manufacturer's recommendation range.

In the cold drug storage units that had a temperature comparable to the manufacture's recommended temperature range for all the refrigerated anaesthetic drugs (2^0C – 8^0C). The time intervals that this temperature range was maintained was a minimum of one temperature measurement and a maximum of 9 hours and 30 minutes with an average time of

4 hours and 30 minutes. (The number of measurements that fulfilled the manufacturers' recommended temperature range is summarised per theatre in Appendix E)

The temperature at which the refrigerated drugs were stored within the main storage refrigerator before and after packaged in the cold drug storage unit for each theatre were recorded at 07:00 and 17:30 for the five days of data collection. Of the ten temperature measurements, with a minimum of 6,4^{0}C, median of 6,9^{0}C and maximum of 8,5^{0}C, only one temperature measurement was outside of the manufacturer's recommended temperature storage range of 2^{0}C – 8^{0}C.

Secondary outcome results

The theatre room temperatures, taken at the same fixed time slots as the cold drug storage unit temperature readings are displayed in the Figure 6. The room temperatures of the theatre suites had an overall combined range of 18,5^{0}C to 25,7^{0}C (with a median of 22,4^{0}C).

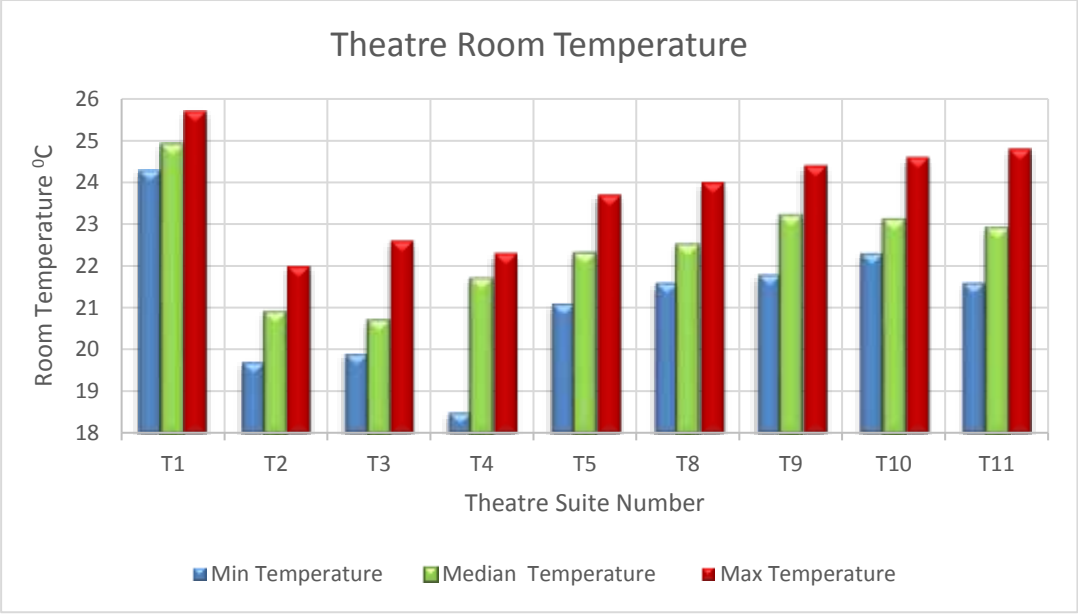

Figure 6: The temperature range of the theatre room temperature summarised per theatre for the five days of data collection

The storage method the anaesthetic personnel used to place the drugs within the cold drug storage unit is displayed in Figure 7

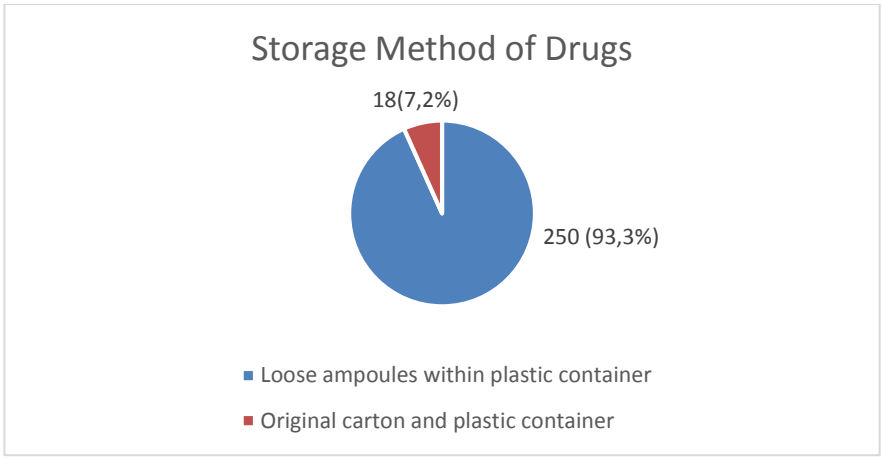

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Figure 7: The storage method of placing drugs within the cold drug storage unit

The eutectic gel packs; the number, size and position within the Styrofoam® Box was noted to not be placed in a standardised manner by the anaesthetic personnel. The various options used are illustrated in Figure 8.

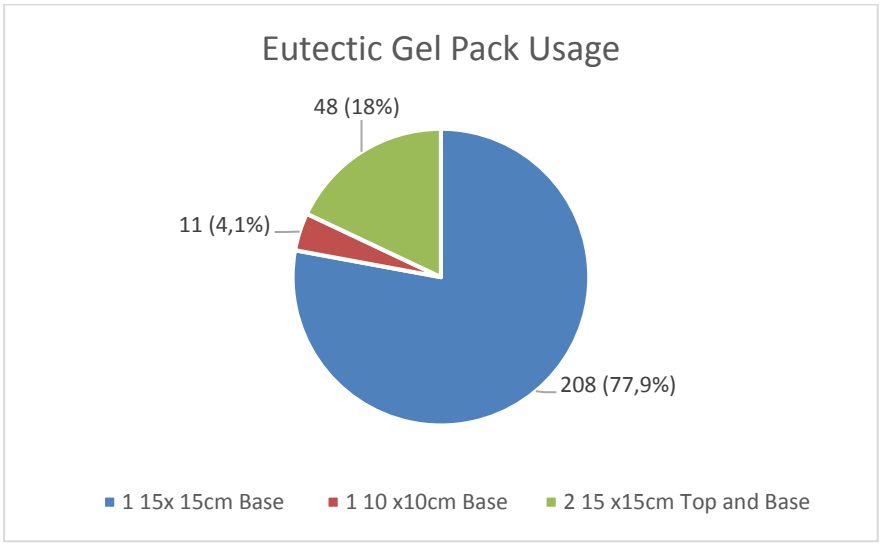

Figure 8: The number of eutectic gel packs use, the size of the gel pack, and the placement of the eutectic gel pack at the base or both on top and at the base of the drugs within the Styrofoam®

The number of ampoules/vials were counted after a cold drug storage unit temperature measurement was taken for an individual theatre per time slot for each day of data collection. Figure 9 depicts the median number of ampoules/vials placed within the cold drug storage unit for each theatre for the five days of the week and the median number of ampoules/vials used in a particular theatre for the five days of the week.

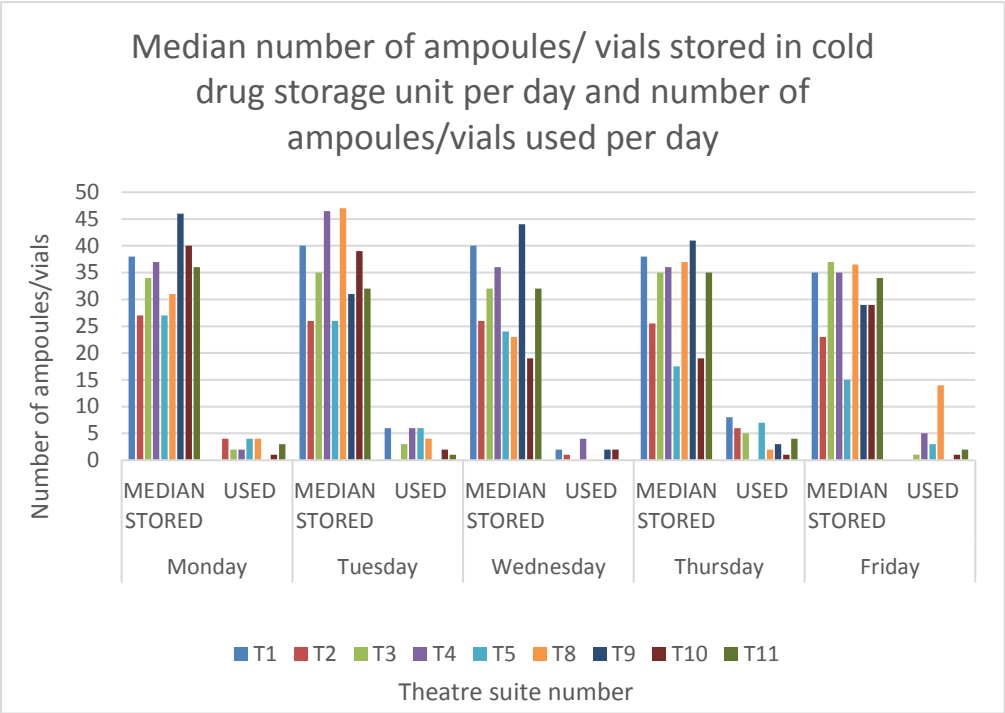

Figure 9: The median number of ampoules/ vials stored in cold drug storage unit per day and absolute number of ampoules/vials used per day per theatre

The data displayed in figure 9 illustrates that a larger proportion of ampoules/vials is removed from the regulated main storage refrigerator and placed within the cold drug storage unit within theatre suites than what is utilised by the anaesthetist on a daily basis.

The contribution of the aforementioned variables contribute to the cold drug storage unit in achieving a temperature range recommended by the manufacturer's (2^0C – 8^0C) compared to the cold drug storage unit not fulfilling the manufacturers' recommended storage range is depicted in Table II.

Table II: Comparison of variables contributing to cold drug storage unit having a temperature $2^0C - 8^0C$ (adequate for storage of temperature sensitive drugs) and more than 8^0C (inadequate for storage of temperature sensitive drugs)

	Adequate storage temperature $2^0C - 8^0C$	**Inadequate storage temperature** ➢ **8^0C**
Total cold drug temperature measurements (n = 267)	32 (12%)	235 (88%)
Theatre room temperature ^0C (Minimum – Median – Maximum)	$20,1^0C - 21,8^0C - 24,6^0C$	$18,5^0C - 22,6^0C - 25,7^0C$
Numbers of ampoules/vials (Minimum – Median – Maximum)	23 – 35 – 46	15 – 34 – 53
Storage method used		
Plastic container	90,6%	94%
Plastic container & original carton	9,4%	6%
Eutectic Gel pack usage		
One 15 cm x 15 cm placed at the base	0	208 (88,5%)
One 10 cm x 10 cm placed at the base	0	11 (4,7%)
Two 15 cm x 15 cm placed at the base and on top	32 (100%)	16 (6,8%)
Theatre in use	48,4%	38,7%

The theatre room temperature and the amount of ampoules or vials within the cold drugs storage units were not remarkable different. When the Chi-square Test and Fischer's Exact Test analysis was applied to the variables presented in the table, the storage method used ($p < 0,49$) and the theatre utilization ($p < 0,44$) was not a statistically significant factor contributing to the cold drug storage unit achieving an adequate temperature range to store all the temperature sensitive drugs. The statistical significant factor contributing to the cold drug storage unit maintaining an adequate temperature

range of $2^0C - 8^0C$ was the use of two 15cm x 15cm eutectic gel pack placed on the base and the top of the plastic container housing the drugs within the cold drug storage unit ($p < 0.001$)

The fluctuations in two consecutive cold drug storage temperature measurement were analysed for the greatest increase and the greatest decrease in temperature amongst all nine theatres per day. This fluctuations in temperature is illustrated in Figure 10.

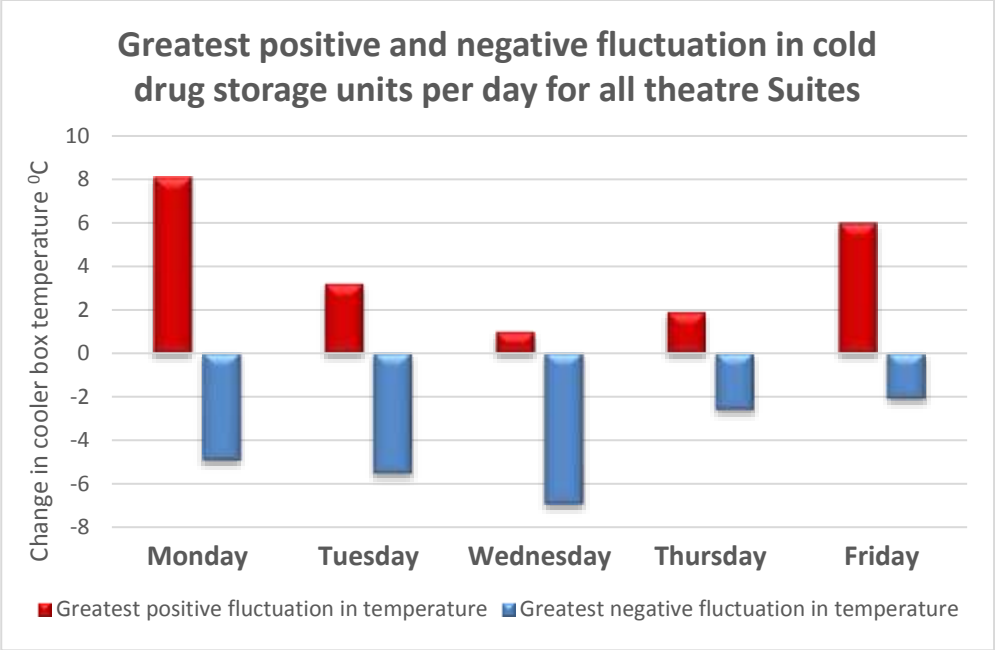

Figure 10: Greatest positive and negative fluctuation, amongst two consecutive temperature readings in the cold drug storage units for all theatres per day

The accompanying factors that could affect these temperature fluctuation are noted in Appendix D.

Discussion

In this descriptive observational study we set out to investigate whether the refrigerated anaesthetic drugs stored in operating theatre suites at UAH, during the workday, are stored at the recommended manufacturer's storage temperature. The importance of access to these refrigerator drugs for the anaesthetist in the individual operating theatres has led to a well-recognised practice of placing these drugs in a non-temperature regulated cold drug storage

unit. With this study we demonstrate that 88% (235 of the 267) of the cold drug storage unit temperature measurements were inadequate to store all the refrigerated drugs according to the manufacturer's recommendations.

The primary objective in this study was to measure the temperature within the cold drug storage units and to assess whether the measured temperature adhered to the manufacturers' temperature storage recommendation. . When analysing the cold drug storage unit temperature measurements taken on 267 occasions during the data collection period an overall temperature range of $4{,}3^0C - 23{,}8^0C$ with a median of $14{,}8^0C$ was recorded. The package leaflets of the temperature sensitive anaesthetic drugs were reviewed for the manufacturer's storage temperature recommendation and it was determined that in order to store all these drugs within the same cold storage drug unit within theatre suits the temperature within this cold drug storage unit should be $2^0C - 8^0C$.This storage temperature measured was found to only adhere to the manufacturer's recommendation to store all the refrigerated anaesthetic drugs on 32 of 267 measurements (12%), therefore 88% (95% Confidence Interval of 83,6% to 91,4%) of the temperature measurement did not comply with recommendation set by the manufacturer. When correcting for the $\pm 1^0C$ accuracy of the digital thermometer used, only 41 (15, 4%) measurements adhere to the manufacturers' temperature storage range.

The secondary objective was to explore whether the following variables; theatre room temperature, the method of storing drugs within the cold drug storage, the size, amount and placement of the eutectic gel packs within the cold drug storage unit, the number of ampoule/vials placed within the cold drug storage unit and theatre utilisation contributed to the measured cold drug storage unit temperature When exploring the factors that could contribute to this cold drug storage units temperature adhering to the manufacturers recommendation the following factors seem to have no significant influence; theatre room temperature, the number of ampoule/vials placed within the cold drug storage unit, the method of storing drugs within the cold drug storage unit and whether theatre was utilised or not. (Refer to Table II)

The size, number and placement of the eutectic gel packs within the cooler box was the main contributor to ensuring a cold drug storage unit temperature below 8^0C ($p < 0{,}001$). It was observed that in all 32 occasions that the cold drug storage unit maintained a temperature range conducive for storing all refrigerated anaesthetic drugs ($2^0C - 8^0C$); two 15cm x15cm gel packs were used, one placed at the base inside the cooler box (at the bottom of the plastic container housing the drugs) and one placed on top of the plastic container. With this eutectic gel pack configuration the temperature can be maintained at $2^0C - 8^0C$ for an average of 4 hours 30 minutes to a maximum of 9 hour 30 minutes during the theatre work day.

An additional secondary outcome was to assess whether the aforementioned variables had any relationship or correlation to the fluctuations in cold drug storage unit temperature noted. The maximum fluctuations between consecutive temperature readings, in all theatres throughout the five days, were a maximum increase in 8^0C to a maximum decrease in $6,9^0$C. (Refer to Figure 10). No clear factor was strongly identified with these large fluctuations noted in consecutive temperature measurements of the cold drug storage unit with regards to the time of day of the greatest fluctuation, the theatre temperature change, the number of ampoules/vials removed, the storage method of the drugs within the cold drug storage unit. A trend was noted in the cold drug storage units amongst an increase in temperature fluctuation when a change in eutectic ice pack from two to one took place. An opposite decrease trend in temperature measurements was noted when an eutectic ice pack was added (from one to two eutectic ice packs) within the cold drug storage unit.

The need to store refrigerated drugs in a non-refrigerated environment in the medical sphere is not unique to anaesthetic practice.[14, 16]. The strategies that have been employed to optimise temperature control for storage of these drugs in critical care transport and aviation teams include high technology coolers, small portable refrigerators and placement within a Packit cooler.[14] The latter method is similar to our current practice in theatre suites at Universitas Academic Hospital. When the effectiveness of this medication storage strategy was tested in the critical care transport industry it was concluded that this industry accepted strategy was not able to maintain the drugs at manufacturer recommended temperature for trip durations lasting longer than 3 hours.[14]

Another component of medical practice requiring storage of temperature sensitive medications outside of a refrigerator is during the transport of immunisations. The cold chain; a system needed to ensure storage of vaccines in temperature regulated conditions, is critical to ensure the required potency of these sensitive biological products.[16] In the absence of a refrigerator the World Health Organisation recommends the storage of these vaccines within either a cold box (maintaining temperature below 10^0C for five to seven days), vaccine box (maintain temperature below 10 ^{0}C for 18 – 50 hours) with adjuncts such as water packs and foam packs.[16]

As the temperature of the cold drug storage unit was inadequate to store all refrigerated drugs 88% of temperature reading, with large fluctuations in temperature on a daily basis, an important practical application is to expose as minimal number of drugs to these non-conducive storage temperatures. From this study it was noted that a median number of ampoule/vials packaged in theatre operating suites were 34 ampoules/vials per theatre per day with the absolute number of ampoules/vials used ranging from 0 – 14, with a median of two.

This study can now add to the existing literature on practical ways in which temperature sensitive drugs required for anaesthesia can be stored during the workday in operating theatre suites that do not have a refrigerator. The suggestion can be made to use two standardised (15cm x15cm) frozen eutectic gel pack placed at the bottom and on top of a plastic container housing the drugs within a Styrofoam® cooler box. As this maintains an internal environment of below 8^0C for an average of 4 hours and 30 minutes and maximum time of 9 hours and 30 minutes, a recommendation can be made to replenish the eutectic gel packs every 4 hours and 30 minutes. This study results and the suggested configuration to maintain and cold drug storage unit temperature of 2^0C – 8^0C can be utilised and implemented as part of an audit assessing the temperature at which temperature sensitive anaesthetic drugs are stored within theatre suites.

With this study we could advocate cold drug storage units in individual operating suites have a temperature display that will alert the nursing staff and anaesthetist when the temperature exceeds the manufacturer's recommendation of 2^0C – 8^0C.This would encourage staff to ensure adequate closure of the cold drug storage unit thereby limiting its exposure to room air and to replenish or add the eutectic gel packs as required..

This study has only focused on drug storage temperature as a main determinant for degradation, but other factors such as light exposure, rotation from exposure to fluctuation in temperature during the course of the day can also result in drug degradation. For this reason future degradation studies can be performed on the refrigerated drugs stored in this manner to determine whether the degree of degradation could be sufficient to result in a loss of potency.

The limitations of this study is that it is a observational study and therefore the Hawthorne effect on nursing practice when packaging the anaesthetic drugs in the cold drug storage unit could influenced the results obtained. The nursing staff, anaesthetist and the participants were not blinded to the temperature display indicating the cold drug storage unit temperature. Additional factors possibly influencing cold drug storage unit temperature could not be accounted for; the number of times a cooler box is opened and whether on closing it was completely sealed. The temperature readings of the cold drug storage unit, although of display on the digital thermometer screen throughout the five consecutive days, were only documented at six time slots from 07:30 – 17:00. The body of supporting literature on the use of a cooler box and ice packs as a means of passive refrigeration in theatre operating suites to store refrigerated anaesthetic drugs are minimal and therefore there are a number of sources used to supplement this study which are older than 5 years.

To ensure that the anaesthetist has easy access to all anaesthetic agents the storage of temperature sensitive anaesthetic drugs are placed within a cooler box with a eutectic gel pack within the operating theatre suites. In this study this well practised, yet ill-defined method in anaesthetic practice guideline[2, 3, 4], was used to determine whether the storage of refrigerated anaesthetic drugs are stored according to manufactures temperature storage recommendation in operating theatres suites at Universitas Academic Hospital. Eight-eight percent of temperature measurements did not maintain a temperature range of 2^0C – 8^0C required to store all required temperature sensitive drugs according to the manufacturer's recommendation. When this storage method adhered to the prescribed temperature range, it contained two eutectic gel packs, above and below the drugs, and maintained a temperature below 8^0C for an average of 4 hours and 30 minutes, up to 9 hours and 30 minutes, in a maximum theatre temperature of 25,7^0C. These findings can The potential success of the specific configuration of the two eutectic gel packs to maintain a temperature conducive with the manufacturer's recommendations highlights the potential for further research in order to implement a local standard operating procedure and support recommendation in anaesthetic practice guidelines in a resource limited environment.

Publishable Manuscript word count without references: 5060

Publishable Manuscript word count including references: 5431

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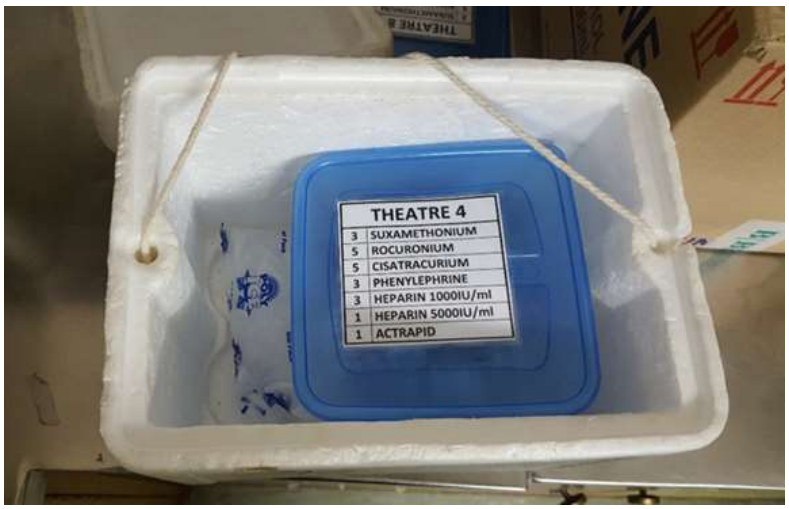
Appendices

A: Cold drug storage unit (Cooler Box and Eutectic Gel pack)



B: Drug Package Information Leaflet

Please note that within the time frame of protocol submission and data collection a few anaesthetic drugs have been purchased by other manufacturers as originally name in the protocol. Attached are the package information leaflet of the drugs available during the time of data collection

Additional drugs stored in the cold drug storage units were Syntometrine®, Phenytoin (the latter is not conventionally placed in the cold drug storage units for individual theatre suites).

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

Suxamethonium Chloride Fresenius 100 mg/2 ml

Injection

COMPOSITION

Each 2 ml ampoule contains:

Active ingredient

Suxamethonium chloride	100 mg

Inactive ingredients

Sodium hydroxide 10 %	qs
Nitrogen	qs
Water for injection	2 ml

PHARMACOLOGICAL CLASSIFICATION

A 17.1 Peripherally-acting muscle relaxants.

PHARMACOLOGICAL ACTION

Suxamethonium chloride is a depolarising, neuromuscular blocking agent. The initial effect is to depolarise the membrane in the same manner as acetylcholine, but more persistently, which results in a brief period of firing manifested by transient muscular fasciculation. This phase is succeeded shortly by neuromuscular paralysis; the mechanism and even the primary site of which are still uncertain and controversial.

INDICATIONS

- to facilitate endotracheal intubation, bronchoscopy and oesophagoscopy, in combination with general anaesthesia with respiratory support
- to obtain rapid, short-term muscle relaxation in various orthopaedic procedures, such as the correction of dislocations and the alignment of fractures, with respiratory support
- as an adjuvant in surgical anaesthesia to obtain relaxation of skeletal muscle, particularly of the abdominal wall, so that operative manipulations are facilitated.

CONTRAINDICATIONS

Patients with a history of hypersensitivity to suxamethonium chloride or to any of the components of **Suxamethonium Chloride Fresenius**.

Patients who have suffered burns, massive trauma, exhibit myotonia and muscular rigidity, hemiplegia, paraplegia, muscular denervation and muscular dystrophies.

A family history of malignant hyperthermia.

Patients with renal impairment with a raised plasma-potassium concentration, severe long-lasting sepsis and severe hyperkalaemia.

Patients with glaucoma, penetrating wounds of eye or while the globe is open, or after initial surgery in massively traumatised patients.

Patients who are known to have atypical pseudocholinesterase.

In patients with low serum-pseudocholinesterase concentrations such as may occur in liver disease, malnutrition, severe anaemia, cancer, collagen diseases, severe dehydration, severe infections, myocardial infarctions, myxoedema, renal impairment and in persons exposed to organophosphate insecticides or weed killers.

In patients with advanced myasthenia gravis, neurological defects or phaeochromocytoma.

WARNINGS AND SPECIAL PRECAUTIONS

Suxamethonium Chloride Fresenius is contraindicated in patients with burns, massive trauma, renal impairment with a raised plasma-potassium concentration, severe lung-sepsis and severe hyperkalaemia.

It is not generally recommended in uraemic patients especially those with high serum-potassium concentrations.

Caution is required when **Suxamethonium Chloride Fresenius** is given to patients with cardiac or respiratory disease or to those that have shown hypersensitivity to any neuromuscular blocker.

Hypothermia may enhance the neuromuscular blocking effects of **Suxamethonium Chloride Fresenius** and an increase in body temperature may reduce them.

Children may be at special risk from cardiac arrest associated with hyperkalaemia.

Suxamethonium Chloride Fresenius should be used with caution in patients with reduced pseudocholinesterase activity as it may prolong suxamethonium paralysis

There have been reports of prolonged neuromuscular blockade following the use of **Suxamethonium Chloride Fresenius** in patients receiving lithium.

A repeat dose of Suxamethonium Chloride Fresenius within a short time (of the initial dose) may precipitate a vagal cardiac arrest. A rapidly acting anticholinergic agent (atropine) should be administered.

Malignant hyperpyrexia may occur. **Suxamethonium Chloride Fresenius** is a trigger agent for this accelerated hypermetabolic syndrome; it occurs in subjects with musculoskeletal disorders and also in apparently healthy individuals who are genetically predisposed to this syndrome. The symptoms are an increased respiratory carbon dioxide output, tissue hypoxia, usually but not necessary an increasing body temperature with or without muscular hypertonicity, often fatal cardiovascular complications, severe acidosis, hyperkalaemia and haemoglobinuria or myoglobinuria. Immediate treatment is required. Administer dantrolene sodium intravenously and treat the symptoms.

INTERACTIONS

Many medicines may interact with **Suxamethonium Chloride Fresenius**.

The mechanism of action may be due to a direct effect on neuromuscular transmission or an alteration of enzyme activity.

Suxamethonium Chloride Fresenius may interact with the following substances to produce prolonged paralysis: some aminoglycoside or polypeptide antibiotics including gentamycin, tobramycin, amikacin, clindamycin, lincomycin, polymyxins, tetracyclines, magnesium sulphate, narcotic analgesics, quinidine, cyclophosphamide, cimetidine, metoclopramide, phenelzine, oestrogens, tamoxifen, nifedipine and verapamil.

Following reports of apnoea, caution has been advised when aprotinin and neuromuscular blockers such as **Suxamethonium Chloride Fresenius** are used concomitantly.

Intravenous use of **Suxamethonium Chloride Fresenius** may develop tachyphylaxis and phase II block when inhalation anaesthetics are used. Neuromuscular blockers such as **Suxamethonium Chloride Fresenius** are potentiated in a dose-dependent manner by inhalation anaesthetics, and the dose may need to be reduced depending on the anaesthetic used and its concentration.

Bradycardia due to **Suxamethonium Chloride Fresenius** may be enhanced by inhalation agents such as halothane.

Administration of **Suxamethonium Chloride Fresenius** before or after the use of non-polarising relaxants may cause a mixed block.

Procaine and cocaine may competitively enhance the neuromuscular blocking activity of **Suxamethonium Chloride Fresenius**. The depolarising effects of **Suxamethonium Chloride Fresenius** may also be enhanced by neostigmine and other anticholinesterases; it has been recommended that eye drops containing a long-acting anticholinesterase should be discontinued at least 2 weeks before the administration of **Suxamethonium Chloride Fresenius**.

The effects of digitalis may be enhanced by **Suxamethonium Chloride Fresenius**, leading to cardiac dysrhythmias.

There have been reports of prolonged neuromuscular blockade following the use of **Suxamethonium Chloride Fresenius** in patients receiving lithium (see "Warnings and Special precautions").

PREGNANCY AND LACTATION

The safety of **Suxamethonium Chloride Fresenius** has not been established in pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE

Atropine could be considered before administration of **Suxamethonium Chloride Fresenius** to prevent excessive bradycardia, bronchial secretion, or other muscarine effects. The recommended dose is 1 – 2 mg/kg intravenously.

SIDE EFFECTS

Immune system disorders

Frequencies unknown:

Hypersensitivity reactions to **Suxamethonium Chloride Fresenius** have been reported and bronchospasm has occurred.

Nervous system disorders

Frequencies unknown:

Prolonged neuromuscular blockade and apnoea may occur in patients with low serum concentrations of pseudocholinesterase and in those with an atypical pseudocholinesterase. The same conditions could result when excessive amounts of **Suxamethonium Chloride Fresenius** accumulate at the neuromuscular junction, for example following high or repeated doses. The nature of the block may change to one with characteristics similar to competitive block. This is known as phase II block.

Eye disorders

Frequencies unknown:

Suxamethonium Chloride Fresenius may cause a transient rise in intra-ocular pressure.

Cardiac disorders

Frequencies unknown:

Stimulation of the vagus nerve and parasympathetic ganglia by **Suxamethonium Chloride Fresenius** may be followed by bradycardia, other dysrhythmias, and hypotension. This may be exacerbated by the raised plasma-potassium concentration. Cardiac arrest has been reported.

Tachycardia and an increase in blood pressure due to stimulation of sympathetic ganglia has also been reported. Tachyphylaxis may occur with repeated doses.

Respiratory, thoracic and mediastinal disorders

Frequencies unknown:

There may be some increase in bronchial secretions due to the muscarinic action of **Suxamethonium Chloride Fresenius.**

Prolonged apnoea occurs in patients with low serum concentrations of pseudocholinesterase and in those with an atypical pseudocholinesterase.

Gastrointestinal disorders

Frequencies unknown:

A transient rise in intra-gastric pressure may occur secondary to abdominal muscle fasciculation. There may be some increase in bowel movements and in gastric and salivary secretions due to the muscarinic action of **Suxamethonium Chloride Fresenius**. Salivary gland enlargement may occur.

Musculoskeletal, connective tissue and bone disorders

Frequencies unknown:

The administration of **Suxamethonium Chloride Fresenius** results in transient fasciculations during the onset of depolarising block. Rhabdomyolysis, myoglobinaemia and myoglobinuria have been reported and may be associated with muscle damage following fasciculations.

Muscular pain similar to that following strenuous exercise may occur in the immediate postoperative period, particularly in patients who are ambulant but it is not related to dosage or the degree of fasciculation.

Plasma cholinesterase concentrations also fall during pregnancy and the puerperium and therefore maternal paralysis may be mildly prolonged.

General disorders and administration site conditions

Frequencies unknown:

Depolarisation of skeletal muscle produces an immediate increase in plasma-potassium concentration and this can have serious consequences in some patients.

Direct release of histamine from mast cells occurs and flushing, skin rash, bronchospasm and shock have been reported.

Malignant hyperpyrexia (see "Warnings and Special precautions").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See above for symptoms.

Prolonged apnoea should be treated until spontaneous respiration is fully restored.

A synthetic cholinesterase may be given to remove **Suxamethonium Chloride Fresenius**. Neostigmine should not be used.

When the action of **Suxamethonium Chloride Fresenius** is prolonged, the myoneural block may cease to be depolarising in type and may acquire some features of the paralysis produced by non-depolarising muscle relaxant agent, i.e. dual block. In these cases controlled ventilation should be continued until spontaneous respiration is fully restored.

IDENTIFICATION

Clear solution in amber glass ampoules.

PRESENTATION

Packs of 10 x 2 ml ampoules.

STORAGE INSTRUCTIONS

Store in a refrigerator (2 - 8 °C).

Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

M/17.1/270

NAME AND BUSINESS ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION

BODENE (PTY) LIMITED trading as Intramed
6 Gibaud Road
Korsten
Port Elizabeth
South Africa
6020

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Last approved: 25 November 2011

12-427/03-16

Prescription only Medicine (POM)

Botswana: BOT0600843, S2

Namibia NS2, 90/17.1/00441

Zimbabwe: 1.3 Cholinesterase inhibitors and muscle relaxants used in anaesthesia 2003/1.3/4119, PP

Kenya: 14380, POM

Tanzania: TAN06, 253 NO4A BOD, POM

Zambia: 254/028, POM

SCHEDULING STATUS
S4

PROPRIETARY NAME AND DOSAGE FORM
ROCURONIUM 50 IV BIOTECH (injection)

COMPOSITION
ROCURONIUM 50 IV BIOTECH: Each 5 ml vial contains 50 mg rocuronium bromide.
Another ingredients: Sodium acetate, sodium chloride, glacial acetic acid, sodium hydroxide and water for injections.

PHARMACOLOGICAL CLASSIFICATION
A 17.1 Peripherally acting muscle relaxants.

PHARMACOLOGICAL ACTION
Pharmacodynamics:
Rocuronium is a non-depolarising neuromuscular blocking agent. It acts by binding with the nicotinic acetylcholine receptor at the motor end-plate. The ED_{90} (dose required to produce 90 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0,3 mg per body mass.
The clinical duration (the duration until spontaneous recovery to 25 % of control twitch height) with 0,6 mg per kg body mass is 30 – 40 minutes. The total duration (time until spontaneous recovery to 90 % of control twitch height) is 58 minutes. The mean time of spontaneous recovery of twitch response from 25 – 75 % (recovery index) after a bolus dose of 0,6 mg rocuronium bromide per kg body mass is 14 minutes. With lower dosages of 0,5 – 0,45 rocuronium bromide per kg body mass ($1 - 1,5\ xED_{95}$), onset of action is slower and duration of action is shorter (13 and 26 minutes).

Pharmacokinetics:
After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration time-course runs in three exponential phases. In normal adults, the mean (95 % CI) elimination half-life is 73 (66-80) minutes; the (apparent) volume of distribution at steady state conditions is 203 (193 – 214) $ml.kg^{-1}$ and plasma clearance is 3,7 (3,5 – 3,9) $ml.kg^{-1}.min^{-1}$. The plasma clearance in elderly patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic diseases, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 $ml.kg^{-1}.min^{-1}$. When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased.
A large between patient variability is found in controlled clinical studies, related to subject extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean ($t_{1/2\beta}$) elimination half-life of 21,5 (± 3,1) hours, a (apparent) volume of distribution at steady state of 1,3 (± 0,8) $l.kg^{-1}$ and a plasma clearance of 2,1 (± 0,8) $ml.kg^{-1}.min^{-1}$ was found.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40 % within 12 – 24 hours. After injection of radio-labelled dose of rocuronium bromide, excretion of radio-labelled rocuronium is on average 47 % in urine and 43 % in faeces after 9 days. Approximately 50 % is recovered as the parent compound.

INDICATIONS
ROCURONIUM 50 IV BIOTECH is indicated as an adjunct:
- to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction and to provide skeletal muscle relaxation during surgery,
- in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation for up to 3 days in adults 18 – 65 years of age.

CONTRA-INDICATIONS
ROCURONIUM 50 IV BIOTECH is contraindicated in:
- Patients hypersensitive to rocuronium or the bromide ion.
- Neonates (0 – 1 month).
- ICU circumstances for the facilitation of mechanical ventilation in paediatric and geriatric patients.
- Pregnancy and lactation.
- Caesarean section.

WARNINGS and SPECIAL PRECAUTIONS

Since ROCURONIUM 50 IV BIOTECH causes paralyses of respiratory muscles, ventilatory support is mandatory for patients treated with ROCURONIUM 50 IV BIOTECH until adequate spontaneous respiration is restored. It is important to anticipate intubation difficulties particularly when used as part of a rapid sequence induction technique.

Severe anaphylactic reactions to rocuronium, as in ROCURONIUM 50 IV BIOTECH have been reported. These reactions have, in some cases been fatal. Due to the possible severity of these reactions, it should be assumed that they may occur and the necessary precautions should be taken. Cross-sensitivity reactions to similar neuromuscular blocking agent may occur. Since ROCURONIUM 50 IV BIOTECH is capable of inducing histamine release both locally at the site of injection and systemically, possible occurrence of itching and erythematous reactions at the site of injection and/or general generalised histaminic-release reactions should be taken into consideration when administering ROCURONIUM 50 IV BIOTECH. The most frequent reaction to ROCURONIUM 50 IV BIOTECH consists of an extension of the medicine's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea.

Neuromuscular blocking agents are known to be capable of inducing histamine release both locally and systemically. This should be taken into consideration when administering ROCURONIUM 50 IV BIOTECH due to the possible occurrence of itching and erythematous reactions at the injection site, and/or general anaphylactoid reaction (bronchospasm and cardiovascular changes).

In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block with train-of-four (TOF) of 0,9 or above. Other factors which could cause residual neuromuscular blockade after extubation in post-operative phase (such as medicine interactions or patient condition) should also be considered, especially in those cases where residual neuromuscular blockade is more likely to occur (see "Dosage and Directions for use").

Muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced doctors who are familiar with their actions and with appropriate neuromuscular monitoring techniques.

Adequate analgesia and sedation should be given to the patients.

Prolonged paralysis and/or skeletal muscle weakness has been noted following long term treatment of muscle relaxants in the ICU. It is strongly recommended that neuromuscular transmission be monitored throughout the treatment period in order to help preclude possible prolongation of neuromuscular block and/or overdosage.

ROCURONIUM 50 IV BIOTECH is always used concurrently with other agents and malignant hyperthermia can occur during anaesthesia (even in the absence of known triggering agents). Therefore, the doctor should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of ROCURONIUM 50 IV BIOTECH.

Prolonged circulation time:
Conditions (such as cardiovascular disease, old age, and oedematous state resulting in an increased volume of distribution) that prolong circulation time, may contribute to a slower onset of action.

Hepatic and/or biliary tract disease and renal failure:
Special caution is advised when administering ROCURONIUM 50 IV BIOTECH to patients with hepatic and/or biliary diseases and/or renal failure. As ROCURONIUM 50 IV BIOTECH is excreted in urine and bile, prolongation of action has been observed with doses of 0,6 mg ROCURONIUM 50 IV BIOTECH per kg of body mass.

Hypothermia:
The neuromuscular blocking effect of ROCURONIUM 50 IV BIOTECH is increased and prolonged during surgery under hypothermic conditions.

Burns:
Patients with burns are known to develop resistance to non-depolarising neuromuscular blocking agents. It is recommended that the dose be titrated to response.

Neuromuscular disease:
Extreme caution is advised in patients with neuromuscular disease or after poliomyelitis, as the response to neuromuscular blocking agents can be altered in these cases. The magnitude and direction of the alteration may vary widely. Small doses of ROCURONIUM 50 IV BIOTECH in patients with myasthenia gravis or with the myasthenic syndrome, can have profound effects. ROCURONIUM 50 IV BIOTECH should be titrated to the response.

Obesity:
A prolonged duration and prolonged spontaneous recovery in obese patients are exhibited when the administered doses are calculated on actual body mass.

Conditions which may increase the effects of ROCURONIUM 50 IV BIOTECH:
Hypokalaemia, hypermagnesaemia, hypocalcaemia, hypoproteinaemia, dehydration, acidosis, hypercapnoea, cachexia. Altered blood pH, dehydration and severe electrolyte disturbances should therefore be corrected when possible.

Effects on ability to drive and use machines:
The use of potentially dangerous machinery or driving a car is not recommended within 24 hours after the full recovery from the neuromuscular blocking action.

INTERACTIONS
The neuromuscular blocking activity of aminoglycosides, bacitracin, colistin, polymyxins, sodium colistimethate, tetracyclines or vancomycin may be additive to that of ROCURONIUM 50 IV BIOTECH.

Concurrent administration of inhalation halogenated anaesthetics with ROCURONIUM 50 IV BIOTECH, results in additive neuromuscular blocking activity. The infusion rate of ROCURONIUM 50 IV BIOTECH should be reduced by 40 % when used concurrently with enflurane and isoflurane.

The following agents will also enhance the neuromuscular blockade of ROCURONIUM 50 IV BIOTECH:
- Large doses of magnesium salt
- High doses of thiopentone, methohexitone, ketamine, fentanyl, etomidate and propofol
- Other antibiotics (Enacoxamide, polypeptide antibiotics, acylaminopenicillin, high doses metronidazole)
- Diuretics, thiamine, mono-amine oxidase (MAO) inhibiting agents, quinidine, protamine, α-adrenergic blocking agents, calcium channel blocking agents and lithium salts.

Variable effects:
- Administration of other non-depolarising neuromuscular blocking agents in combination with ROCURONIUM 50 IV BIOTECH may produce attenuation or potentiation of neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.
- Suxamethonium given after administration of ROCURONIUM 50 IV BIOTECH may produce potentiation or attenuation of neuromuscular blocking effects of ROCURONIUM 50 IV BIOTECH.

A decrease in the neuromuscular blockade of ROCURONIUM 50 IV BIOTECH occurs when the following agents are used concurrently:
- Prior chronic treatment with corticosteroids, phenytoin or carbamazepine.
- Theophylline, potassium chloride, calcium chloride, norepinephrine (noradrenalin) and azathioprine.
- Aminopyridine derivatives, pyridostigmine, edrophonium and neostigmine.
- Protease inhibitors.

Incompatibilities
Physical incompatibilities have been noted for ROCURONIUM 50 IV BIOTECH when added to solutions containing the following: amphotericin, amoxycillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methicillin, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. ROCURONIUM 50 IV BIOTECH is also incompatible with Intralipid®.

PREGNANCY AND LACTATION
ROCURONIUM 50 IV BIOTECH is contraindicated during pregnancy and lactation (see "Contraindications").

DOSAGE AND DIRECTIONS FOR USE
Dosage
The dosage of ROCURONIUM 50 IV BIOTECH should be individualised in each patient.

The following should be taken into account when determining the dose:
- method of anaesthesia and the expected duration of surgery,
- the method of sedation and the expected duration of mechanical ventilation,
- the possible interaction with other medication that is administered concomitantly,
- the condition of the patient.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Inhalation anaesthetics potentiate the neuromuscular blocking effects of ROCURONIUM 50 IV BIOTECH. Potentiation, however, becomes clinically relevant in the course of anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with ROCURONIUM 50 IV BIOTECH should be made by:

- administering smaller maintenance doses at less frequent intervals or
- by using lower infusion rates of ROCURONIUM 50 IV BIOTECH during long lasting procedures (longer than 1 hour) under inhalation anaesthesia (see "Interactions").

In adult patients the following dosage recommendations serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

Surgical procedures
Tracheal intubation
The standard intubating dose during anaesthesia is 0,6 mg ROCURONIUM 50 IV BIOTECH per kg body mass, after which adequate intubation conditions are established within 90 seconds.

A dose of 1 mg ROCURONIUM 50 IV BIOTECH per kg body mass is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia. At this dose adequate intubation conditions are established within 60 seconds in nearly all patients.

A twitch suppression of 90 % or a train-of-four (TOF) of 1 or less must be obtained prior to intubation. Disappearance of the TOF will correspond to optimal intubation conditions.

Maintenance dosing
The recommended maintenance dose is 0,15 mg ROCURONIUM 50 IV BIOTECH per kg body mass. The maintenance doses should best be given as a bolus when twitch height has recovered to 25 % of control twitch height, or when 2 to 3 responses to train-of-four (TOF) stimulation are present.

The duration of action of maintenance doses of 0,15 mg ROCURONIUM 50 IV BIOTECH per kg body mass will be longer under enflurane and isoflurane anaesthesia in elderly patients, and in patients with hepatic disease and/or renal disease (approximately 20 minutes), than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes).

Continuous infusion
If ROCURONIUM 50 IV BIOTECH is administered by continuous infusion, it is recommended to give a loading dose of 0,6 mg ROCURONIUM 50 IV BIOTECH per kg body mass and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10 % of control twitch height or to maintain 1 to 2 responses to train-of-four stimulation. In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0,3 – 0,6 mg.kg^{-1}.h^{-1} and under inhalation anaesthesia the infusion rate ranges from 0,3 – 0,4 mg.kg^{-1}.h^{-1}. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Reversal of muscle relaxation
On completion of the surgical procedure where ROCURONIUM 50 IV BIOTECH was administered, anti-cholinesterase agents such as neostigmine, pyridostigmine or edrophonium is used to reverse and decrease the duration of competitive neuromuscular blockade. A muscarinic antagonist (atropine or glycopyrrolate) is used concomitantly to prevent stimulation of muscarinic receptors and thereby to avoid slowing of the heart rate.

Administration of sugammadex (a chelating agent specific for rocuronium and vecuronium) at doses > 2 mg/kg is able to reverse neuromuscular blockade from ROCURONIUM 50 IV BIOTECH within 3 minutes. In patients with impaired renal function, sugammadex clearance is markedly reduced and this agent should be avoided.

Before administering a neuromuscular antagonist, the train-of-four count should be at least 3.

The TOF count should preferably be done with a monitoring device.

Dosing in paediatric patients
Children (1 – 14 years) and infants (1 – 12 months) under halothane anaesthesia manifest similar sensitivity to ROCURONIUM 50 IV BIOTECH as adults. Onset of action is faster in infants and children than in adults. Clinical duration is shorter in children than in adults.

Dosing in overweight and obese patients
When used in overweight or obese patients (defined as patients with a body weight of 30 % or more above ideal body mass) doses should be reduced taking into account a lean body mass.

Intensive care procedures
Tracheal intubation
For tracheal intubation, the same doses should be used as described above under surgical.

Dosing to facilitate mechanical ventilation
The use of an initial loading dose of 0,6 mg ROCURONIUM 50 IV BIOTECH per kg body mass is recommended, followed by a continuous infusion as soon as twitch height recovers to 10 % or upon reappearance of 1 to 2 twitches to train-of-four (TOF) stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80 – 90 % (1 to 2 twitches to train-of-four (TOF) stimulation) in adult patients is 0,3 – 0,6 mg.kg^{-1}.h^{-1} during the first hour of administration, which will need to be decreased during the following 6 – 12 hours, according to individual response.

Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found, with mean hourly infusion rates ranging from 0,2 – 0,5 mg.kg^{-1}.h^{-1} depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal and individual patient control, monitoring of neuromuscular transmission is strongly recommended. Safety and efficacy beyond 3 days has not been established.

Following continuous infusion in the Intensive Care Unit, the time to recovery of the train-of-four ratios to 0,7 depends on the level of block at the end of the infusion. After a continuous infusion of 20 hours or more, the median (range) time between return of T_2 to train-of-four stimulation and recovery of the train-of-four ratios to 0,7 approximates 1,5 (1 – 5) hours in patients without multiple organ failure and 4 (1 – 25) hours in patients with multiple organ failure. Spontaneous respiration is only recommended when the TOF is 0,9.

Administration
ROCURONIUM 50 IV BIOTECH is administered intravenously either as a bolus injection or as a continuous infusion.

Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0,5 mg/ml and 2 mg/ml ROCURONIUM 50 IV BIOTECH has been shown to be compatible with: 0,9 % NaCl, 5 % dextrose, 5 % dextrose in saline, sterile water for injection, Lactated Ringer's.

Administration should begin immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

ROCURONIUM 50 IV BIOTECH can be injected into the intravenous line of a running infusion with solution of the following intravenous medicines: epinephrine (adrenaline), alcuronium, alfentanil, aminophylline, atracurium, atropine, cefuroxime, ceftriaxone, cimetidine, clemastine, clindamycin, clomethiazole, clonazepam, clonidine, diazepam, dobutamine, dopamine, dehydrobenzperidol, ephedrine, ergometrine, esmolol, etomidate, fentanyl, flucytosine, gentamycin, glucose 40 %, glycopyrronium bromide, heparin, hydralazine, ketamine, labetalol, lignocaine, mannitol 20 %, metoclopramide, metoprolol, metronidazole, midazolam, milrinone, morphine, nifedipine, nimodipine, nitroglycerine, norepinephrine (noradrenaline), oxytocin, pancuronium, pethidine, pipecuronium, potassium chloride, promethazine, propranolol, propofol, ranitidine, salbutamol, sodium carbonate, sodium nitroprusside, sufentanil, suxamethonium, vecuronium and verapamil.

Also refer to incompatibilities header under "Interaction" section.

SIDE EFFECTS
Immune system disorders
Less frequent: Anaphylactic reaction; hypersensitivity; angioedema; increase in mean plasma histamine.

Cardiac disorders
Less frequent: Dysrhythmia; tachycardia.

Vascular disorders
Less frequent: Hypertension; hypotension; flushing.

Respiratory, thoracic and mediastinal disorders
Less frequent: Bronchospasm; wheezing.

Skin and subcutaneous tissue disorders
Less frequent: Pruritus; skin rash; erythematous rash.

General disorders and administration site conditions
Frequent: Pain at injection site.
Less frequent: Swelling at injection site; facial oedema.

Gastrointestinal disorders
Less frequent: Hiccups; nausea; vomiting.

Musculoskeletal disorders
Frequent: Muscle weakness, myopathy; injury, poisoning and procedural complications.
Less frequent: Prolonged neuromuscular block, delayed recovery from anaesthesia, airway complication of anaesthesia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
The acute effects of an overdose are apnoea and prolonged paralysis.

The patient should continue to receive controlled ventilation and sedation until spontaneous recovery. Acetylcholinesterase inhibitors (pyridostigmine, neostigmine, edrophonium) should be administered in adequate doses. If these agents fail to reverse the neuromuscular block of ROCURONIUM 50 IV BIOTECH, ventilation should be continued until spontaneous breathing is restored. Repeated doses of acetylcholinesterase inhibitors can be dangerous.

Further treatment should be supportive and symptomatic.

IDENTIFICATION
A clear, colourless to yellow or orange solution.

PRESENTATION
ROCURONIUM 50 IV BIOTECH is filled into a clear Type I glass vials with dark grey rubber stopper and aluminium cap. 10 x 5 ml or 1 x 5 ml vials per outer carton.

STORAGE INSTRUCTIONS
Store between 2-8 °C. Protect from light.
Do not freeze.
Keep vial in outer carton until required for use.
Since ROCURONIUM 50 IV BIOTECH does not contain any preservative, it should be used immediately after first opening the container and any unused solution should be discarded.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
44/17.1/0188

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
BIOTECH LABORATORIES (PTY) LTD.
Ground Floor, Block K West, Central Park
400 16th Road, Randjespark, Midrand, 1685
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT
04 November 2014

PI.44/0188/1

TRACRIUM®

SCHEDULING STATUS: 1000000141588

S4

PROPRIETARY NAME AND DOSAGE FORM:
TRACRIUM® Injection 2,5 ml (solution for injection)
TRACRIUM® Injection 5,0 ml (solution for injection)
Excipients: benzene sulphonic acid and water for injections.

COMPOSITION:
Each ampoule of 2,5 ml contains 25 mg atracurium besylate.
Each ampoule of 5,0 ml contains 50 mg atracurium besylate.

PHARMACOLOGICAL CLASSIFICATION:
A 17.1 Peripherally-acting muscle relaxants

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
TRACRIUM is a selective, competitive (non-depolarising) neuromuscular blocking agent.

Pharmacokinetic properties:
TRACRIUM is degraded mainly by spontaneous non-enzymatic decomposition (Hofmann elimination) which occurs at body pH and temperature into inactive metabolites. The termination of the neuromuscular blocking action of TRACRIUM is not dependent on metabolism and excretion by the liver or kidneys. The duration of action is therefore unlikely to be affected by impaired renal, hepatic or circulatory function. Variations in the blood pH and body temperature of the patient within the pathological range may alter the duration of action of TRACRIUM. It is possible that some decomposition may occur by non-specific plasma esterases. Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of TRACRIUM proceeds unaffected. TRACRIUM has no effect on the intra-ocular pressure.
When administered to laboratory animals in high doses, laudanosine, a metabolite of atracurium, has been associated with transient hypotension and, in some species, cerebral excitatory effects. Although seizures have been seen in ICU patients receiving atracurium, a causal relationship to laudanosine has not been established (see WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS:
TRACRIUM is used in anaesthesia to relax skeletal muscles and to facilitate controlled ventilation. TRACRIUM is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

CONTRA-INDICATIONS:
Known hypersensitivity to atracurium besylate.

WARNINGS AND SPECIAL PRECAUTIONS:
TRACRIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES, BUT HAS NO EFFECT ON CONSCIOUSNESS. THEREFORE IT SHOULD BE ADMINISTERED ONLY WITH ADEQUATE ANAESTHESIA AND ONLY BY OR UNDER THE CLOSE SUPERVISION OF AN ANAESTHETIST AND ADEQUATE FACILITIES MUST BE AVAILABLE FOR ENDOTRACHEAL INTUBATION AND ARTIFICIAL VENTILATION.
MONITORING OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED DURING THE USE OF TRACRIUM IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.
The potential exists for histamine release in susceptible patients. Caution should be exercised in administering TRACRIUM to patients with a history suggestive of an increased sensitivity to the effects of histamine.
TRACRIUM should be used with caution in patients with myasthenia gravis, other neuromuscular diseases and severe electrolyte disorders in which potentiation of other non-depolarising agents has been noted.
Resistance to non-depolarising neuromuscular blocking agents may develop in burn patients. Increased doses of non-depolarising muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.
In limited clinical studies, in patients susceptible to

Where a small vein is selected as the injection site, TRACRIUM should be flushed through the vein with physiological saline after injection. Where other anaesthetic medicines are administered through the same in-dwelling needle or cannula as TRACRIUM, it is important that each medicine is flushed through with physiological saline.
The dosage range recommended for adults is 0,3 to 0,6 mg/kg depending on the duration of complete neuromuscular block (full block) required and will provide muscle relaxation for 15 to 35 minutes. Complete neuromuscular block (full block) can be prolonged with supplementary doses of 0,1 to 0,2 mg/kg as required. Successive supplementary dosing does not give rise to accumulation. Endotracheal intubation can usually be accomplished within 90 seconds from the intravenous injection of 0,5 to 0,6 mg/kg. The neuromuscular block produced by TRACRIUM can be rapidly reversed by standard doses of anti-cholinesterase agents such as neostigmine and edrophonium preceded or accompanied by atropine, with no evidence of recurarization. Recovery from the end of complete neuromuscular block (full block) without use of neostigmine occurs in about 35 minutes as measured by restoration of the tetanic response to 95 % of normal neuromuscular function.

Use in Infusion:
After an initial bolus dose of 0,3 to 0,6 mg/kg, TRACRIUM can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion at rates of 0,3 to 0,6 mg/kg/hr (0,005 to 0,01 mg/kg/minute). Accurate dosage administration of the infusion may be achieved using a syringe pump. TRACRIUM can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25-26 °C reduces the rate of inactivation, therefore full neuromuscular block may be maintained by approximately half the original infusion rate at these low temperatures. TRACRIUM is compatible with the following infusion solutions for the times stated below:

Infusion Solution	Period of Stability
Sodium Chloride Intravenous BP (0,9 % m/v)	24 hours
Glucose Intravenous BP (5 % m/v)	8 hours
Ringers Injection USP	8 hours
Sodium Chloride (0,18 % m/v) and Glucose (4 % m/v) Intravenous Infusion BP	8 hours
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution)	4 hours

When diluted in these solutions to give atracurium concentrations of 0,5 mg/ml to 0,9 mg/ml, infusions of TRACRIUM are stable in daylight at temperatures of up to 30 °C.

Dosage in children:
The dosage requirements in children aged one month and over are similar to those in adults on a mg/kg basis.

Dosage in Elderly and High risk Patients:
TRACRIUM may be used at standard dosage in elderly patients and in those with cardiac, respiratory, renal (including end-stage failure) or hepatic failure. In elderly patients it is recommended, however that the initial dose be at the lower end of the range and that it be administered slowly. Patients with clinically significant cardiovascular disease may be more susceptible to the effects of transient hypotension. In these patients slow intravenous injection in divided doses over a period of 1-2 minutes is recommended. TRACRIUM should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.

Long-term use in Intensive Care Units (ICU):
TRACRIUM has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the risk-benefit ratio of neuromuscular blockade must be considered. Available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that TRACRIUM infusion requirements may increase with prolonged administration in the ICU. The effects of haemodialysis, haemoperfusion and haemofiltration on plasma levels of atracurium and its metabolites are unknown.

SIDE EFFECTS:
TRACRIUM does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, TRACRIUM has no clinically significant

malignant hyperthermia, TRACRIUM has not triggered this syndrome.
TRACRIUM is hypotonic and must not be administered into the infusion line of a blood transfusion.

Intensive Care Unit (ICU) Patients:
There have been reports of seizures in ICU patients who have been receiving atracurium concurrently with several other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). A causal relationship to laudanosine has not been established. In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.
There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids. These events have been seen infrequently in association with TRACRIUM and a causal relationship has not been established.

INTERACTIONS:
The neuromuscular block produced by TRACRIUM may be increased by the concomitant use of inhalation anaesthetics such as halothane, isoflurane and enflurane.
The neuromuscular block produced by TRACRIUM may be increased by the concomitant use of:

- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- antiarrhythmic medicines: propranolol, calcium channel blockers, lignocaine, procainamide and quinidine
- diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide
- magnesium sulphate
- ketamine
- lithium salts
- ganglion blocking agents: trimetaphan, hexamine.

Certain medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to TRACRIUM would be consequent on such development. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmic medicines (procainamide, quinidine), antirheumatic medicines (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.
The onset of non-depolarising neuromuscular block is likely to be lengthened and the duration of block shortened in patients receiving chronic anticonvulsant therapy. The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with TRACRIUM may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of TRACRIUM administered.
Any synergistic effect may vary between different medicines combinations. A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarizing agents such as TRACRIUM, as this may result in a prolonged and complex block which can be difficult to reverse with anti-cholinesterase drugs.

PREGNANCY AND LACTATION:
Use in pregnancy and obstetrics:
Safety during the course of pregnancy has not been established. TRACRIUM is suitable for maintenance of muscle relaxation during Caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses. It is not known whether TRACRIUM is excreted into human milk.

DOSAGE AND DIRECTIONS FOR USE:
Use by Injection:
TRACRIUM is administered by intravenous injection. It must not be mixed with thiopentone or any alkaline agents as the high pH would cause inactivation of the TRACRIUM.

effects on heart rate in the recommended dosage range and it will not counteract the bradycardia produced by many anaesthetic agents and by vagal stimulation during surgery. There have been reports of skin flushing, instances of transient hypotension and bronchospasm, which may be due to histamine release. Anaphylactoid reactions have also been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Signs: Prolonged muscle paralysis and its consequences are the main signs of overdosage.
Treatment: It is essential to maintain a patent airway together with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. Recovery may be hastened by the administration of anti-cholinesterase agents accompanied by atropine or glycopyrrolate, once evidence of spontaneous recovery is present.

IDENTIFICATION:
2,5 ml and 5,0 ml ampoules containing a clear faint yellow solution for intravenous administration.

PRESENTATION:
Box of 5 x Ampoules of 2,5 ml.
Box of 5 x Ampoules of 5,0 ml.

STORAGE INSTRUCTIONS:
Keep out of reach of children.
Store at 2 to 8 °C. Do not freeze.
Protect from light.
Open ampoules of TRACRIUM should be discarded immediately after use.

REGISTRATION NUMBER:
TRACRIUM Injection 2,5 ml: R/17.1/209
TRACRIUM Injection 5,0 ml: R/17.1/210

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:
GlaxoSmithKline South Africa (Pty) Ltd
39 Hawkins Avenue
Epping Industria 1
7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:
27 August 1998

GDS-13

TRACRIUM is a registered trade mark of the **GSK** group of companies

Botswana

TRACRIUM® Injection 2,5 ml: Reg No. B9316845 S2
TRACRIUM® Injection 5,0 ml: Reg No. B9316850 S2

Namibia

TRACRIUM® Injection 2,5 ml: Reg No. 90/17.1/00585 NS2
TRACRIUM® Injection 5,0 ml: Reg No. 90/17.1/00586 NS2

Zimbabwe

TRACRIUM® Injection 2,5 ml: Reg No. 84/1.3/1848 PP
TRACRIUM® Injection 5,0 ml: Reg No. 84/1.3/1848 PP

NIMBEX®

10000000119098

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:
NIMBEX® 2 mg/ml (2,5 ml) injection
NIMBEX® 2 mg/ml (5 ml) injection
NIMBEX® 2 mg/ml (10 ml) injection
NIMBEX® 5 injection

COMPOSITION:
Each NIMBEX 2 mg/ml (2,5 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.
Each NIMBEX 2 mg/ml (5 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.
Each NIMBEX 2 mg/ml (10 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.
Each NIMBEX 5 vial contains cisatracurium 5 mg/ml, as the besylate.

PHARMACOLOGICAL CLASSIFICATION:
A 1.1.1 Peripherally-acting muscle relaxants.

PHARMACOLOGICAL ACTION:
Cisatracurium is an intermediate-duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant. Cisatracurium binds to cholinergic receptors on the motor-end-plate to antagonise the action of acetylcholine, resulting in a competitive block at neuromuscular transmission. This action is readily reversed by anticholinesterase agents such as neostigmine or edrophonium.
Pharmacokinetic properties:
Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites. These metabolites do not possess neuromuscular blocking activity.
Pharmacokinetics in Adult Patients: The ED_{95} dose required to produce 95 % depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of cisatracurium is estimated to be 0,05 mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam). The ED_{95} of cisatracurium besylate in children during halothane anaesthesia is 0,04 mg/kg.
Non-compartmental pharmacokinetics of cisatracurium are independent of dose in the range studied (0,1 to 0,2 mg/kg; i.e. 2 to $4xED_{95}$). Pharmacokinetic parameters after doses of 0,1 and 0,2 mg/kg NIMBEX Injection administered to healthy adult surgical patients are summarised in the table below.

Parameter	Range of mean values
Clearance	4,7 to 5,7 ml/min/kg
Volume of distribution at steady state	121 to 161 ml/kg
Elimination half-life	22 to 29 min

Pharmacokinetics in Elderly Patients: There are no clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients.
Pharmacokinetics in Patients with Renal Impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure and in healthy adult patients. The recovery profile of cisatracurium is unchanged in the presence of renal failure.
Pharmacokinetics in Patients with Hepatic Impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage liver disease and in healthy adult patients. The recovery profile was unchanged.
Pharmacokinetics During Infusions: The pharmacokinetics of cisatracurium after infusions of NIMBEX Injection are similar to those after single bolus injection. The recovery profile after infusion of NIMBEX Injection is independent of duration of infusion and is similar to that after single bolus injections.
Pharmacokinetics in Intensive Care Unit (ICU) Patients: The pharmacokinetics of cisatracurium in ICU patients receiving prolonged infusions are similar to those in healthy surgical adults receiving infusions or single bolus injections. The recovery profile after infusions of NIMBEX Injection in ICU patients is independent of duration of infusion. When laudanosine was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation. However, there is no evidence that laudanosine has caused such effects in man even after prolonged infusions of cisatracurium to ICU patients with impaired renal and/or hepatic function.

INDICATIONS:
NIMBEX is used during surgical procedures to relax skeletal muscles and to facilitate controlled ventilation. NIMBEX is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

CONTRA-INDICATIONS:
NIMBEX Injection is contra indicated in patients known to be hypersensitive to cisatracurium, atracurium, or benzenesulphonic acid.
Use and safety in pregnancy and lactation has not been established.
Neonates, as NIMBEX Injection has not been studied in this patient population.

WARNINGS:
CISATRACURIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES BUT HAS NO EFFECT ON CONSCIOUSNESS OR PAIN THRESHOLD. NIMBEX INJECTION SHOULD ONLY BE ADMINISTERED BY OR UNDER THE SUPERVISION OF AN ANAESTHETIST. FACILITIES FOR TRACHEAL INTUBATION AND MAINTENANCE OF PULMONARY VENTILATION AND ADEQUATE ARTERIAL OXYGENATION MUST BE AVAILABLE. MONITORING OF NEUROMUSCULAR FUNCTION IS RECOMMENDED DURING THE USE OF NIMBEX INJECTION IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.
NIMBEX is hypotonic and must not be administered into the infusion line of a blood transfusion.
ICU Patients: When laudanosine, a metabolite of cisatracurium, was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation.

DOSAGE AND DIRECTIONS FOR USE:
Use by intravenous bolus injection:
Dosage in adults:
Tracheal Intubation: The recommended intubation dose of NIMBEX Injection for adults is 0,15 mg/kg. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection. Higher doses will shorten the time to onset of neuromuscular block. The following table summarises mean pharmacodynamic data when NIMBEX Injection was administered at doses of 0,1 to 0,4 mg/kg to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90 % T_1* Suppression (min)	Time to Maximum T_1* Suppression (min)	Time to 25 % Spontaneous T_1* Recovery (min)
0,1	Opioid	0,4	4,8	45
0,15	Propofol	2,6	3,5	55
0,2	Opioid	2,4	2,9	60
0,4	Opioid	1,5	1,9	91

* Single twitch response as well as the first component of the Train-of-Four response of the adductor pollicis muscle following supramaximal electrical stimulation of the ulnar nerve.

Maintenance: Neuromuscular block can be extended with maintenance doses of NIMBEX Injection. A dose of 0,03 mg/kg provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anaesthesia. Consecutive maintenance doses do not accumulate.

Infusion Delivery Rate of NIMBEX Injection 2 mg/ml

Patient Weight (kg)	Dose (µg/kg/min)				Infusion Rate
	1,0	1,5	2,0	3,0	
30	0,6	0,9	1,2	1,8	ml/hr
70	2,1	3,2	4,2	6,3	ml/hr
100	3,0	4,5	6,0	9,0	ml/hr

Steady rate continuous infusion of NIMBEX Injection is not associated with a progressive increase or decrease in neuromuscular blocking effect.
Following discontinuation of infusion of NIMBEX Injection, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.
Dosage in neonates aged less than 1 month:
No dosage recommendation for neonates can be made until further information becomes available.
Dosage in elderly patients:
No dosing alterations are required in elderly patients. In these patients NIMBEX Injection has a similar pharmacodynamic profile to that observed in young adult patients, but as with other neuromuscular blocking agents, it may have a slightly slower onset.
Dosage in patients with renal impairment:
No dosing alterations are required in patients with renal failure. In these patients, NIMBEX Injection has a similar pharmacodynamic profile to that observed in patients with normal renal function, but it may have a slightly slower onset.
Dosage in patients with hepatic impairment:
No dosing alterations are required in patients with end-stage liver disease. In these patients NIMBEX Injection has a similar pharmacodynamic profile to that observed in patients with normal hepatic function but it may have a slightly faster onset.
Dosage in patients with cardiovascular disease:
NIMBEX has been used to provide neuromuscular block in patients undergoing cardiac surgery. When administered by rapid bolus injection (over 5 to 10 seconds) to patients with serious cardiovascular disease, NIMBEX has not been associated with clinically significant cardiovascular effects in any dose studied (up to and including 0,4 mg/kg (6x ED_{95})).
Dosage in Intensive Care Unit (ICU) patients:
NIMBEX Injection may be administered by bolus dose and/or infusion to adult patients in the ICU. An initial infusion rate of NIMBEX Injection at 3 µg/kg/min (0,18 mg/kg/hr) is recommended for adult ICU patients. There may be wide interpatient variation in dosage requirements and these may increase or decrease with time. In clinical studies the average infusion rate was 3 µg/kg/min (range 0,9 to 10,2 µg/kg/min (0,05 to 0,6 mg/kg/hr)). The median time to full spontaneous recovery following long-term (up to 5 days) infusion of NIMBEX Injection in ICU patients was approximately 52 minutes.

Infusion Delivery Rate of NIMBEX Injection 5 mg/ml

Patient Weight (kg)	Dose (µg/kg/min)				Infusion Rate
	1,0	1,5	2,0	3,0	
70	0,8	1,2	1,7	2,5	ml/hr
100	1,2	1,8	2,4	3,6	ml/hr

The recovery profile after infusions of NIMBEX Injection to ICU patients is independent of duration of infusion.
Dosage in patients undergoing hypothermic cardiac surgery:
There have been no studies of NIMBEX Injection in patients undergoing surgery with induced hypothermia (25 to 28 °C). The rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.
Dilution:
Diluted NIMBEX Injection is physically and chemically stable for at least 12 hours at 3 °C and 35 °C at concentrations between 0,1 and 2,0 mg/ml in the following infusion fluids, in either polyvinyl chloride (PVC) or polypropylene containers:
Sodium Chloride 0,9 % m/v Intravenous Infusion, Glucose 5 % m/v Intravenous Infusion, Sodium Chloride (0,18 % m/v) and Glucose (4 % m/v) Intravenous Infusion, Sodium Chloride (0,45 % m/v) and Glucose (2,5 % m/v) Intravenous Infusion.
However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, administration should commence as soon as possible thereafter and any remaining solution should be discarded.
NIMBEX Injection is not chemically stable when diluted with Lactated Ringer's Injection.
NIMBEX Injection has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port: alfentanil hydrochloride, droperidol, fentanyl citrate, midazolam hydrochloride and sufentanil citrate. Where other drugs are administered through the same indwelling needle or cannula as NIMBEX Injection, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g. Sodium Chloride Intravenous Infusion 0,9 % m/v).
Since NIMBEX Injection is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions, e.g. sodium thiopentone. It is not compatible with ketorolac, tromethamol or propofol injectable emulsion.
When a small vein is selected as the injection site, NIMBEX Injection should be flushed through the vein with a suitable intravenous fluid, e.g. Sodium Chloride Intravenous Infusion (0,9 % m/v).

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
No adverse experiences occurred during the clinical development programme that were considered to be reasonably attributable to NIMBEX Injection. Adverse experiences, considered possibly attributable, occurred with a frequency of less than 0,5 %. These were cutaneous flushing or rash, bradycardia, hypotension and bronchospasm.
Severe anaphylactic reactions have been reported in patients receiving NIMBEX in conjunction with one or more anaesthetics.
There have been some reports of persistent muscle weakness and/or myopathy following prolonged use of NIMBEX in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids.
Precautions:
Great caution should be exercised when administering NIMBEX Injection to patients who have shown allergic hypersensitivity to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents has been reported.
Cisatracurium does not have significant vagolytic or ganglion-blocking properties. Consequently, NIMBEX Injection has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.
Patients with myasthenia gravis and other forms of neuromuscular disease have shown greatly increased sensitivity to non-depolarising blocking agents. An initial dose of not more than 0,02 mg/kg NIMBEX Injection is recommended in these patients.
Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents.
NIMBEX Injection has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that cisatracurium does not trigger this syndrome.
Cisatracurium has not been studied in patients with burns; however, as with other non-depolarising neuromuscular blocking agents, the possibility of increased dosing requirements and shortened duration of action must be considered if NIMBEX Injection is administered to these patients.
Interactions:
Many drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents, including the following:
Increased effect:
Anaesthetics: Volatile agents such as enflurane, isoflurane and halothane.
Ketamine.
Other non-depolarising neuromuscular blocking agents.
Other drugs:
- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- anti-arrhythmic drugs, including propranolol, calcium channel blockers, lignocaine, procainamide and quinidine
- diuretics, including furosemide and possibly thiazides, mannitol and acetazolamide
- magnesium salts
- lithium salts

not result in progressive prolongation of effect.
Spontaneous Recovery: Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the NIMBEX dose. During opioid or propofol anaesthesia, the median times from 25 to 75 % and from 5 to 95 % recovery are approximately 12 and 30 minutes, respectively.
Reversal: Neuromuscular block following NIMBEX administration is reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75 % recovery and to full clinical recovery ($T_4:T_1$ ratio ≥0,7) are approximately 4 and 9 minutes respectively, following administration of the reversal agent at an average of 10 % T_1 recovery.

Dosage in paediatric patients aged 1 month to 12 years:
Tracheal Intubation: As in adults, the recommended intubation dose of NIMBEX Injection is 0,15 mg/kg administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of NIMBEX. Pharmacodynamic data for this dose are presented in the tables below. If a shorter clinical duration is required, pharmacodynamic data suggest that a dose of 0,1 mg/kg may produce similar intubation conditions at 120 to 150 seconds.
In paediatric patients aged 1 month to 12 years, NIMBEX has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. Small differences in the pharmacodynamic profile were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarised in the tables below.

Paediatric Patients aged 1 to 11 months:

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90 % Suppression (min)	Time to Maximum Suppression (min)	Time to 25 % Spontaneous T_1 Recovery (min)
0,15	Halothane	1,4	2,0	50
0,15	Opioid	1,4	3,0	47

Paediatric Patients aged 1 to 12 years:

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90 % Suppression (min)	Time to Maximum Suppression (min)	Time to 25 % Spontaneous T_1 Recovery (min)
0,08	Halothane	1,7	2,5	31
0,1	Opioid	1,7	2,5	28
0,15	Halothane	2,3	3,0	43
0,15	Opioid	2,6	3,5	38

Halothane may be expected to extend the clinically effective duration of a dose of NIMBEX by up to 20 %. No information is available on the use of NIMBEX in children during isoflurane anaesthesia but these agents may also be expected to extend the clinically effective duration of a dose of NIMBEX by up to 20 %.
Maintenance: Neuromuscular block can be extended with maintenance doses of NIMBEX Injection. A dose of 0,02 mg/kg provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.
Spontaneous Recovery: Once recovery from neuromuscular block is underway, the rate is independent of the NIMBEX dose administered. During opioid or halothane anaesthesia, the median times from 25 to 75 % and from 5 to 95 % recovery are approximately 11 and 28 minutes, respectively.
Reversal: Neuromuscular block following NIMBEX administration is reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75 % recovery and to full clinical recovery ($T_4:T_1$ ratio ≥0,7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13 % T_1 recovery.

Use by intravenous infusion:
Dosage in adults and children aged 2 to 12 years:
Maintenance of neuromuscular block may be achieved by infusion of NIMBEX Injection. An initial infusion rate of 3 µg/kg/min (0,18 mg/kg/hr) is recommended to restore 90 to 99 % T_1 suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 µg/kg/min (0,06 to 0,12 mg/kg/hr) should be adequate to maintain block in this range in most patients.
Reduction of the infusion rate by up to 40 % may be required when NIMBEX Injection is administered during isoflurane or enflurane anaesthesia (see INTERACTIONS). The infusion rate will depend upon the concentration of cisatracurium in the infusion solution, the desired degree of neuromuscular block, and the patient's weight. The following table provides guidelines for delivery of undiluted NIMBEX Injection.

- ganglion blocking drugs: trimetaphan, hexamethonium.

Decreased effect:
Prior chronic administration of phenytoin or carbamazepine.
Prior administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of NIMBEX Injection or on infusion rate requirements.
Administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases.
Rarely, certain drugs may aggravate or unmask silent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Such drugs include various antibiotics, beta-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and diltiazem.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with NIMBEX Injection.
It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired by NIMBEX Injection. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

IDENTIFICATION:
A clear, pale yellow or greenish yellow solution, free from visible particulate matter.

PRESENTATION:
NIMBEX 2 mg/ml (2,5 ml) Injection: Box of 5 ampoules
NIMBEX 2 mg/ml (5 ml) Injection: Box of 5 ampoules
NIMBEX 2 mg/ml (10 ml) Injection: Box of 5 ampoules
NIMBEX 5: Box with one 30 ml vial

STORAGE INSTRUCTIONS:
Unopened ampoule/vial:
Keep out of reach of children.
Store between 2 °C and 8 °C.
Do not freeze.
Protect from light.
In addition, the diluted solution can be stored at 5 °C or 25 °C.
This product is marketed as a single dose ampoule/vial and any unused portion of the solution must be discarded.
The ampoule/vial must not be removed from the outer carton until such time as it is required for administration.

REGISTRATION NUMBER:
NIMBEX 2 mg/ml (2,5 ml) Injection: 31/17.1/0255
NIMBEX 2 mg/ml (5 ml) Injection: 31/17.1/0444
NIMBEX 2 mg/ml (10 ml) Injection: 31/17.1/0445
NIMBEX 5 Injection: 31/17.1/0256

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:
GlaxoSmithKline South Africa (Pty) Ltd
30 Hawkins Avenue
Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:
27 November 1998

GCS-7

Nimbex:
Nimbex 2 mg/ml (2,5 ml): Reg No 04/17.1/0929 [N52]
Nimbex 2 mg/ml (5 ml): Reg No 04/17.1/0928 [N52]
Nimbex 2 mg/ml (10 ml): Reg No 04/17.1/0927 [N52]
Nimbex 5: Reg No 04/17.1/0926 [N52]

GlaxoSmithKline

SCHEDULING STATUS: S1

PROPRIETARY NAME AND DOSAGE FORM: **PHENYLEPHRINE HYDROCHLORIDE INJECTION (solution for injection)**

COMPOSITION
Each 1 ml ampoule contains 10 mg of phenylephrine hydrochloride.
Excipients: Sodium hydroxide, hydrochloric acid and water for injection. Sugar free.

PHARMACOLOGICAL CLASSIFICATION
7.2 Vasoconstrictors, pressor medicines.

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Phenylephrine is an alpha 1 adrenergic receptor agonist.
After injection phenylephrine produces peripheral vasoconstriction and an increase in arterial pressure; it also produces reflex bradycardia. Beta 1 adrenergic effects are insignificant.

Pharmacokinetic properties
Following an intravenous infusion of phenylephrine hydrochloride, the effective half-life was approximately 5 minutes. The steady-state volume of distribution (340 l) exceeded the body volume by a factor of 5, suggesting a high distribution into certain organ compartments. The average total serum clearance (2095 ml/min) was close to one-third of the cardiac output.

A mass balance study showed that phenylephrine is extensively metabolised by the liver with only 12 % of the dose excreted unchanged in the urine. Deamination by monoamine oxidase is the primary metabolic pathway resulting in the formation of the major metabolite (m-hydroxymandelic acid) which accounts for 57 % of the total administered dose.

INDICATIONS
PHENYLEPHRINE HYDROCHLORIDE INJECTION is indicated for increasing the blood pressure in adults with clinically significant hypotension resulting primarily from vasodilation, in such settings as septic shock or anaesthesia.

The duration of action is short-lived (minutes) and repeat injections are frequently required.

CONTRAINDICATIONS
Hypersensitivity to phenylephrine of any of the components of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** (see **COMPOSITION**).
Paediatric use.
PHENYLEPHRINE HYDROCHLORIDE INJECTION is contraindicated in the presence of severe:
- uncontrolled hypertension
- hyperthyroidism
- heart-block with or without bradycardia
- uncontrolled cardiac failure
- bradycardia (less than 50 bpm)
- or seriously impaired coronary circulation

WARNINGS AND SPECIAL PRECAUTIONS
Sustained IV infusion may result in diminished efficacy.

Cardiovascular effects: Severe bradycardia and decreased cardiac output may occur.
Excessive peripheral and visceral vasoconstriction with ischaemia to vital organs may occur, especially in patients with extensive peripheral vascular disease e.g. Raynaud's phenomenon.
Increased blood pressure may occur and precipitate underlying heart failure, angina in patients with severe arteriosclerosis or past history of angina, and increase pulmonary arterial pressure.
In patients with reduced cardiac output or coronary vascular disease, vital organ functions should be closely monitored and dose reduction should be considered when systemic blood pressure is near the lower end of the target range.

Dermatologic effects: Avoid extravasation as this can cause necrosis or sloughing of tissue.

Endocrine and metabolic effects: Use extreme caution in patients with hyperthyroidism.

Monoamine oxidase (MAO) inhibitors: Concurrent use may prolong and intensify cardiac stimulation and vasopressor effects because of the release of catecholamines which accumulate in intraneuronal storage sites during MAO inhibitor therapy; this may result in headache, cardiac dysrhythmias, vomiting or sudden and severe hypertensive or hyper-pyretic crises.
For patients who have been receiving MAO inhibitors 2 to 3 weeks prior to administration of sympathomimetic medicines, the initial dosage should be reduced to be no more than one-tenth of the usual dose.

Immunologic effects: Allergic reactions, including anaphylactic symptoms, may occur in patients with sulfite-sensitivity.

Neurologic effects: Blood pressure response to **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may be increased in patients with autonomic dysfunction.

Renal toxicity: PHENYLEPHRINE HYDROCHLORIDE INJECTION can increase the need for renal replacement therapy in patients with septic shock. Monitor renal function.

INTERACTIONS
- *Alpha*-adrenergic blocking medicines – concurrent use may antagonise the peripheral vasoconstriction effect of **PHENYLEPHRINE HYDROCHLORIDE INJECTION**. Examples: doxazosin, labetalol, prazosin, haloperidol, phenothiazines.
- The effect of antihypertensive and diuretic medicines used as antihypertensives may be reduced when used concurrently with **PHENYLEPHRINE HYDROCHLORIDE INJECTION**; the patient should be carefully monitored to confirm the desired effect is obtained.
- *Beta*-adrenergic blocking medicines, systemic or ophthalmic – concurrent use of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** in the presence of beta-adrenergic medicines (systemic or ophthalmic) may result in an exaggeration of the vasoconstriction effects and profound bradycardia.
- Digoxin – **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may be used with digoxin for therapeutic advantage; caution and close electrocardiographic monitoring are recommended during concurrent use.
- Other sympathomimetic medicines – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may increase cardiovascular effects and the potential for side effects.
- Monoamine oxidase (MAO) inhibitors such as selegiline, moclobemide, linezolid, nialamide, pargyline, phenelzine – concurrent use may prolong and intensify cardiac stimulation and vasopressor effects (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). This interaction is still possible 15 days after discontinuation of MAO (see **"CONTRAINDICATIONS"**).
- Ergot alkaloids such as bromocriptine, lisuride, carbergoline, pergolide dihydroergotamine, ergotamine, methylergometrine, methysergide – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** increases the risk of vasoconstriction and/or hypertensive crisis.
- Tricyclic antidepressants (e.g. imipramine) and noradrenergic-serotoninergic antidepressants (milnacipram, venlafaxine) – concomitant use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** causes paroxysmal hypertension with possibility of dysrhythmias due to the inhibition of epinephrine (adrenaline) or norepinephrine (noradrenaline) entry in sympathetic fibers.
- Quinidine – concurrent use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** may increase the risk of cardiac dysrhythmias.
- Oxytocic medicines – concomitant use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** potentiates the vasopressor-active effects. Thus, some oxytocic medicines may cause severe persistent hypertension and strokes can occur during post-partum period.
- Reserpine and other sympatholytic medicines – concomitant use with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** causes a substantial increase in blood pressure (hyperreactivity linked to the reduction in sympathetic tone and/or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibers). If the combination cannot be avoided, use with caution.
- The pressor effect of **PHENYLEPHRINE HYDROCHLORIDE** is increased in patients receiving atropine sulfate.

PREGNANCY AND LACTATION
Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE
General dosing information
Patients receiving **PHENYLEPHRINE HYDROCHLORIDE INJECTION** should be closely monitored. Treatment with **PHENYLEPHRINE HYDROCHLORIDE INJECTION** is not a substitute for replacement of blood, plasma, fluids and/or electrolytes. Prior to administration of therapy, hypovolaemia should be corrected. Acidosis may reduce the effectiveness of phenylephrine.
An infusion pump or other suitable metering device should be used to control the rate of infusion in order to avoid unintended administration of a bolus dose. Infusions of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** should be given into a large vein, or preferably, directly into the central venous line. Inspect the solution for particulate matter and discolouration prior to administration. The diluted solution should not be kept for more than 4 hours at room temperature or for more than 24 hours under refrigerated conditions. Discard any unused portion.

PHENYLEPHRINE HYDROCHLORIDE INJECTION is not for intramuscular or subcutaneous use.
Caution is recommended to avoid extravasation, which may cause tissue necrosis and sloughing of surrounding tissues (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). When discontinuing therapy, the dosage should be reduced gradually, since sudden cessation of therapy may result in severe hypotension. Intravascular fluid should be replaced if necessary to avoid hypotension.

Dosage and administration
PHENYLEPHRINE HYDROCHLORIDE INJECTION must be diluted before administration as bolus intravenous infusion or continuous intravenous infusion. Dosage must be adjusted to meet the individual requirements of each patient, on the basis of clinical response. Some patients may need higher than usual recommended doses for a time.

Preparing a 50 mcg/ml Solution of Bolus Intravenous Administration
For bolus intravenous administration, add 10 mg (1 ml of a 10 mg/ml concentration) of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** to 200 ml of 5 % Dextrose Injection or 0,9 % Sodium Chloride Injection. This will yield a final concentration of 50 mcg/ml. Withdraw an appropriate dose from the 50 mcg/ml solution prior to bolus intravenous administration of the diluted solution.

Preparing a Solution for Continuous Intravenous Infusion
For continuous intravenous infusion, withdraw 10 mg (1 ml of 10 mg/ml concentration) of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** and add 500 ml of 5 % Dextrose Injection of 0,9 % Sodium Chloride Injection (providing a final concentration of 20 mcg/ml).

Dosing for Perioperative Setting
In adult patients undergoing surgical procedures with either neuraxial anaesthesia or general anaesthesia:
- 50 mcg to 250 mcg by intravenous bolus administration. The most frequently reported initial bolus dose is 50 mcg or 100 mcg.
- 0,5 mcg/kg/min to 1,4 mcg/kg/min by intravenous continuous infusion, titrated to blood pressure goal.

Dosing for Septic or Other Vasodilatory Shock
In adult patients with septic or other vasodilatory shock:
- 0,5 mcg/kg/min to 6 mcg/kg/min by intravenous continuous infusion, titrated to blood pressure goal. Doses above 6 mcg/kg/min do not show significant incremental increase in blood pressure.

SIDE EFFECTS
PHENYLEPHRINE HYDROCHLORIDE INJECTION can cause side effects.
PHENYLEPHRINE HYDROCHLORIDE INJECTION may cause a transient tingling and coolness of the skin and a temporary sensation of fullness in the head. Extravasation of the injection may cause local necrosis (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
Peripheral vasoconstriction, possibly leading to necrosis or gangrene, may occur with prolonged use of **PHENYLEPHRINE HYDROCHLORIDE INJECTION** in high doses or low doses in the presence of peripheral vascular disease.

Cardiac disorders:
Less frequent: angina, bradycardia, dyspnoea, hypertension, hypotension, tachycardia, and ventricular dysrhythmias

Central nervous system disorders:
Frequent: headache
Less frequent: nervousness or restlessness, insomnia, paresthesia, tremor

Immune system disorders:
Less frequent: Hypersensitivity

Psychiatric disorders:
Less frequent: Anxiety, excitability, agitation, psychotic states, confusion

Eye disorders:
Less frequent: Mydriasis, aggravation of pre-existing angle-closure glaucoma

Vascular disorders:
Less frequent: Cerebral haemorrhage, hypertensive crisis

Respiratory, thoracic and mediastinal disorders:
Less frequent: Dyspnoea, pulmonary oedema

Gastrointestinal disorders:
Less frequent: Nausea, vomiting

Skin and subcutaneous tissue disorders:
Less frequent: Sweating, pallor or skin blanching, piloerection, skin necrosis with extravasation

Musculoskeletal and connective tissue disorders:
Less frequent: Muscular weakness

Renal and urinary disorders:
Less frequent: Difficulty in micturition and urinary retention

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT
Symptoms of overdosage include headache, hypertension (which may be severe), palpitations, nausea and vomiting. For excessive hypertensive effects, the administration should be reduced or the medication temporarily discontinued until blood pressure is decreased. If these measures fail to lower the blood pressure, a short acting alpha-adrenergic blocking medicine may be administered.

IDENTIFICATION
Glass ampoules containing 10 mg **PHENYLEPHRINE HYDROCHLORIDE INJECTION** in 1 ml.

PRESENTATION
5 x 1 ml ampoules packing in a tray and cardboard carton.

STORAGE INSTRUCTIONS
Store at or below 25 °C.
Protect from light. Keep out of reach of children.
Keep covered in carton until time of use.
For single use only. Discard unused portion.

REGISTRATION NUMBER
H830 (Act 101 of 1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Abbott Laboratories S.A. (Pty) Ltd
Abbott Place
219 Golf Club Terrace
Constantia Kloof , 1709

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION
Date of registration: 30 August 1976
Date of most recent amendment to the Professional Information: 13 December 2018

NAME AND ADDRESS OF THE MANUFACTURER OF THE MEDICINE
Biomendi, S.A.
Polígono Industrial de Bernedo s/n
01118 Bernedo (Álava)
SPAIN

Botswana	B9301910	S2
Namibia	14/5.1/0569	NS1

Abbott

PP5ZA/N1

Art. 77036 P9ZA05

Professional Information

SCHEDULING STATUS

S1

PROPRIETARY NAME AND DOSAGE FORM

MINIMS® PHENYLEPHRINE 2,5 % (Drops)
MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 % (Drops)

COMPOSITION (per dispensing unit of 0,5 ml)
MINIMS® PHENYLEPHRINE 2,5 %
Phenylephrine hydrochloride 12,5 mg (2,5 % m/v)
MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %
Phenylephrine hydrochloride 50 mg (10 % m/v)
The inactive ingredients are: Sodium metabisulphite (antioxidant), disodium edetate and purified water.

CATEGORY AND CLASS
A 15.4 Ophthalmic preparations: Other.

PHARMACOLOGICAL ACTION
Pharmacodynamic properties: Phenylephrine hydrochloride is a sympathomimetic amine with a predominantly direct alpha-adrenergic action. Relaxation of the iris sphincter muscle, resulting in mydriasis with little or no cycloplegic effect. Phenylephrine also has an intraocular pressure-lowering effect due to clearing of the influx of aqueous humour. Mydriasis is apparent approximately 15 minutes after drop instillation and maximal after 60-90 minutes. The duration of response is around 5 hours. Ocular use of phenylephrine may result in transconjunctival systemic absorption, leading to systemic cardiovascular reactions.
Pharmacokinetic properties: Systemic absorption is increased when the corneal epithelium is damaged.

INDICATIONS
For ophthalmic purposes **MINIMS® PHENYLEPHRINE 2,5 %** and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** act as mydriatics. They are sometimes used in open-angle glaucoma, to reduce intraocular pressure by virtue of their local vasoconstrictor action, which reduces the production of aqueous humour.

CONTRAINDICATIONS
- Hypersensitivity to phenylephrine, pseudoephedrine or to any of the ingredients of **MINIMS® PHENYLEPHRINE 2,5 %** and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %.**
- In patients with angle-closure glaucoma
- Patients on Monoamine Oxidase Inhibitors (MAOIs), tricyclic anti-depressants and antihypertensive medicines (including beta-blockers).
- Patients on Reversible Inhibitors of Monoamine Oxidase (RIMAs)
- Should not be used in the presence of:
  - severe hypertension as it may cause a prolonged rise in blood pressure
  - hyperthyroidism as it induces tachycardia or reflex bradycardia
  - partial heart block
  - myocarditis
  - bradycardia
  - serious impairment of the coronary circulation.

The 10 % strength is contraindicated:
- in infants and in the elderly
- in patients with cardiac disease or
- in patients with significant hypertension or
- in patients with advanced arteriosclerosis.

WARNINGS AND SPECIAL PRECAUTIONS
MINIMS® PHENYLEPHRINE 2,5 % and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** must be used with caution in patients suffering from severe ischaemic heart disease. Fatalities have been reported in patients with pre-existing cardiovascular disease. The use should also be avoided by patients with diabetes mellitus or prostatic hyperplasia. To reduce the risk of precipitating an attack of narrow angle glaucoma the anterior chamber angle should be evaluated before use. Ocular hyperaemia can increase the systemic absorption of phenylephrine administered topically.
The use of **MINIMS® PHENYLEPHRINE 2,5 %** and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** in the eyes may liberate pigment granules from the iris, especially when given in high doses to the elderly.
Corneal clouding may occur if the corneal epithelium has been denuded or damaged.
MINIMS® PHENYLEPHRINE 2,5 % and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** can cause intense irritation and a local anaesthetic should be instilled into the eye a few minutes beforehand. Systemic absorption may be minimised by compressing the lacrimal sac at the medial canthus for one minute during and after the instillation of the drops. This blocks the passage of the drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa.

Effects on ability to drive and use machines:
The mydriatic effect of phenylephrine can last several hours. Vision impairment may affect the ability to drive and use machines.

INTERACTIONS
Anti-hypertensive medicines:
Topical **MINIMS® PHENYLEPHRINE 2,5 %** and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** should not be used with anti-hypertensive medicines as they may reverse the action of many of these medicines with possibly fatal consequences.
Monoamine Oxidase Inhibitors (MAOIs):
Since phenylephrine is absorbed through the mucosa, interactions may also follow topical application, particularly in patients receiving a MOAI (including a RIMA) e.g. phenelzine and moclobemide. There is an increased risk of adrenergic reactions when used simultaneously with, or up to three weeks after, the administration of MAOIs.
Tricyclic Antidepressants:
The pressor response to adrenergic medicines and the risk of cardiac dysrhythmia may be potentiated in patients receiving tricyclic antidepressants (or within several days of their discontinuation).
Halothane:
Because of the increased risk of ventricular fibrillation, **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** should be used with caution during general anaesthesia with anaesthetics which sensitise the myocardium to sympathomimetics.
Digoxin or Quinidine:
There is an increased risk of dysrhythmias.

HUMAN REPRODUCTION
Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE
Adults and children: to be used as directed by the ophthalmologist.
Use once and discard.

SIDE EFFECTS
Systemic effects are those of sympathetic stimulation.
Immune system disorders
Less frequent: Hypersensitivity and cross-sensitivity to phenylephrine have been reported in a patient hypersensitive to pseudoephedrine.

Eye disorders
Frequent: Acute and chronic allergic conjunctivitis, corneal clouding, irritation (eye pain and stinging) on application to the eye. Blurred vision, photophobia, conjunctival sensitisation and allergy.

Cardiac disorders
Less frequent: Tachycardia or reflex bradycardia (fatal myocardial infarction after the use of **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** in the eye). Palpitations, extrasystoles and cardiac dysrhythmias.

Vascular disorders
Less frequent: Peripheral vasoconstriction and hypertension.
Frequency unknown: Periorbital pallor in preterm patients.

Respiratory, thoracic and mediastinal disorders
Frequency unknown: Pulmonary oedema in paediatric patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
See "SIDE EFFECTS" and "WARNINGS AND SPECIAL PRECAUTIONS".
Because a severe toxic reaction to **MINIMS® PHENYLEPHRINE 2,5 %** and **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %** is of rapid onset and short duration, treatment is primarily supportive. Prompt injection of a rapidly acting alpha-adrenergic blocking medicine such as phentolamine (dose 2 to 5 mg iv) may be considered.

IDENTIFICATION
MINIMS® PHENYLEPHRINE 2,5 % is a clear, colourless solution, reasonably free from visible particulate matter.
MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 % is a clear, colourless solution, reasonably free from visible particulate matter.

PRESENTATION
MINIMS® PHENYLEPHRINE 2,5 %
Sterile, single dose in a polypropylene Minims Body and Minims Cap, disposable eye drops, packed in outer cartons of 20 units, each containing approximately 0,5 ml.
MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %
Sterile, single dose in a polypropylene Minims Body and Minims Cap, disposable eye drops, packed in outer cartons of 20 units, each containing approximately 0,5 ml.

STORAGE INSTRUCTIONS
MINIMS® PHENYLEPHRINE 2,5 %
Store at or below 25 °C, protected from light. **Do not freeze.**
MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %
Store in a refrigerator between 2 – 8 °C protected from light. **Do not freeze.**
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
MINIMS® PHENYLEPHRINE 2,5 %
31/15.4/0450
MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %
0/15.4/22

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Sofiaus (Pty) Ltd
254 Hall Street
Centurion
0157

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION
Date of registration of **MINIMS® PHENYLEPHRINE HYDROCHLORIDE 10 %:** 23 June 1975.
Date of registration of **MINIMS® PHENYLEPHRINE 2,5 %:** 11 June 2015.
Date of current revised professional information: 23 November 2017

SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORM

Heparin Sodium Fresenius 1 000 IU/1 ml
Heparin Sodium Fresenius 5 000 IU/1 ml
Heparin Sodium Fresenius 25 000 IU/1 ml

Injection

COMPOSITION

1 ml ampoule and 5 ml vial containing 1 000 IU/1 ml heparin sodium (mucosal)
1 ml ampoule and 5 ml vial containing 5 000 IU/1 ml heparin sodium (mucosal)
5 ml vial containing 25 000 IU/1 ml heparin sodium (mucosal)
Heparin is obtained from porcine intestinal mucosa.

Inactive ingredients:

- Water for injections
- Preservative: Chlorocresol 0,1% m/v

PHARMACOLOGICAL CLASSIFICATION

A 6.2 Anticoagulants

PHARMACOLOGICAL ACTION

Heparin inhibits the clotting of blood both *in vitro* and *in vivo*. Whole-blood clotting time, thrombin time and one-stage prothrombin time are prolonged, and thromboplastin generation is abnormal. Clotting time is proportional to the concentration of the medicine in the blood. However, with therapeutic doses bleeding time is usually unaffected and a patient can carry on normal activities, such as shaving, without danger of bleeding. The anticoagulant action of the heparin requires the presence of a plasma a-globulin, referred to as "heparin cofactor", a substance that appears to be identical with normal plasma antithrombin (antithrombin III). Heparin does not block prothrombin synthesis in the liver as do the oral anticoagulants but it does inhibit factors involved in the conversion of prothrombin to thrombin. This action is probably exerted by the facilitation of the formation of complexes of the heparin cofactor (antithrombin) with each of the four activated proteases of the coagulation cascade (activated factors IX, X, XI and XII). A similar heparin-stimulated reaction also occurs between antithrombin and thrombin. The detailed mechanism of this phenomenon may involve a heparin-induced conformational change of the inhibitor. It requires 30 to 40 times more heparin to inhibit the action of formed thrombin than it does to prevent thrombin formation. Therefore the prevention of thrombin formation is probably its primary effect. Heparin is not effective after oral or sublingual administration, but it is well absorbed after intramuscular or subcutaneous injection. In the blood it is evenly distributed between white cells and plasma. Heparin disappears exponentially from the circulation at a rate dependent upon the dose. The half-lives of 100, 200 and 400 units/kg, injected intravenously, are 56, 96 and 152 minutes respectively. Heparin is metabolised by the liver and a partially degraded, weakly active form of heparin (unsheparin) is excreted in the urine, after very large intravenous doses, up to 50 % of non-metabolised heparin may appear in the urine. The exact mechanism of renal elimination is unknown.

INDICATIONS

Heparin Sodium Fresenius is used as an anticoagulant in vascular surgery and occasionally in blood transfusions, but its chief use is in the treatment of arterial and venous thrombosis. It may also be used prophylactically after surgery to prevent thromboembolic complications.

CONTRAINDICATIONS

- Known hypersensitivity to heparin, especially when severe heparin-induced thrombocytopenia has occurred in recent months.
- Haemorrhagic blood disorders - especially thrombocytopenia and haemophilia.
- Haemorrhage, active or suspected - especially cerebrovascular, gastrointestinal, except in disseminated intravascular coagulation.
- Conditions where haemorrhage is a particular risk:
  - Aneurysm, cerebral or aortic
  - Hypertension severe or uncontrolled
  - Threatened abortion
  - Recent childbirth
- Subacute bacterial endocarditis
- Pericarditis
- Vasculitis, severe
- Active cavitating tuberculosis
- Visceral carcinoma if there is a possibility of intracranial metastasis
- Peptic ulceration
- During or after eye, brain or spinal cord surgery or trauma
- Prior to lumbar puncture or regional anaesthetic block
- Surgical or traumatic wounds resulting in large open surfaces
- Severe renal function impairment
- Severe hepatic function impairment
- Oesophageal varices

WARNINGS AND SPECIAL PRECAUTIONS

Filter the solution prior to administering the medicine. The filter size must not be more than 20 µm

Haemorrhage

Haemorrhage can occur at virtually any site in patients receiving **Heparin Sodium Fresenius**. An unexplained fall in haematocrit, fall in blood pressure or any other unexplained symptom should lead to serious consideration of a haemorrhagic event. Rarely retroperitoneal haemorrhage can occur even if the clotting time is not prolonged. **Heparin Sodium Fresenius** should be used with extreme caution in disease states in which there is increased danger of haemorrhage, e.g. some vascular purpuras, continuous tube drainage of the stomach or small intestine, menstruation.

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving **Heparin Sodium Fresenius** with a reported incidence of 0 to 30 %. Platelet counts should be obtained at baseline and periodically during **Heparin Sodium Fresenius** administration. Mild thrombocytopenia (count greater than 100 000/mm³) may remain stable or reverse even if **Heparin Sodium Fresenius** is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100 000/mm³ or if recurrent thrombosis develops (see Heparin-induced thrombocytopenia and Heparin-induced thrombocytopenia and thrombosis), the **Heparin Sodium Fresenius** should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin-induced thrombocytopenia (HIT) and Heparin-induced thrombocytopenia and thrombosis (HITT)

Heparin-induced thrombocytopenia (HIT) and Heparin-induced thrombocytopenia and thrombosis (HITT) may occur. Heparin-induced thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets.

HIT may progress to the development of venous and arterial thrombosis, a condition referred to as Heparin-induced thrombocytopenia and thrombosis (HITT). Thrombotic events may also be the initial presentation for HIT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischaemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100 000/mm³ or if recurrent thrombosis develops, the **Heparin Sodium Fresenius** should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Since **Heparin Sodium Fresenius** has caused thrombocytopenia with severe thromboembolic complications, platelet counts should be monitored in patients receiving **Heparin Sodium Fresenius** for more than a few days.

Delayed onset of HIT and HITT

Heparin-induced thrombocytopenia and Heparin-induced thrombocytopenia and thrombosis can occur up to several weeks after the discontinuation of **Heparin Sodium Fresenius** therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of **Heparin Sodium Fresenius** should be evaluated for HIT and HITT.

General

A test dose has been recommended for patients with a history of allergy.

Heparin Sodium Fresenius inhibits the secretion of aldosterone which may cause hyperkalaemia. Plasma potassium levels should be monitored in those patients who are susceptible to hyperkalaemia, especially when receiving **Heparin Sodium Fresenius** for more than 7 days. The problem is normally resolved with the

may therefore increase the risk of haemorrhage include dextrans, thrombolytic enzymes such as streptokinase, high doses of penicillins, some cephalosporins, some contrast media, asparaginase and epoprostenol. Estimations of oral anticoagulant control may be modified by the action of **Heparin Sodium Fresenius** on prothrombin.

Heparin Sodium Fresenius has been reported incompatible with alfacidase, amikacin sulphate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin, cefazolin sodium, cephalexin lactate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, doxorubicin hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulphate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulphate, melicilin sodium, netamicin sulphate, some opioid analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulphate, streptomycin sulphate, tetracycline hydrochloride, tobramycin sulphate, vancomycin hydrochloride and vinblastine sulphate. **Heparin Sodium Fresenius** has also been reported to be incompatible with cisatracurium besilate, tabetasol hydrochloride, levofloxacin, ricardipine hydrochloride, ritodrine and vinorelbine tartrate. Although usually compatible ceftriaxone sodium is reported to inactivate heparin sodium.

PREGNANCY AND LACTATION

Heparin Sodium Fresenius does not cross the placenta and therefore adverse effects on the foetus would not be expected. **Heparin Sodium Fresenius** is considered safer to the foetus than warfarin when used during pregnancy. **Heparin Sodium Fresenius** has not been shown to cause birth defects or bleeding problems in the baby. However, use during the last three months of pregnancy or during the month following baby's delivery may cause bleeding problems in the mother. Heparin does not pass into the breast milk.

DOSAGE AND DIRECTIONS FOR USE

Filter the solution prior to administering the medicine. The filter size must not be more than 20 µm.
Draw up Heparin Sodium Fresenius from the ampoule or vial using the filter provided. Do not use the filter for the administration of Heparin Sodium Fresenius to the patient.
After withdrawal of Heparin Sodium Fresenius from the ampoule or vial, remove the filter and discard appropriately.
Administer Heparin Sodium Fresenius as per prescription using a NEW needle. Do not use filter needle to administer Heparin Sodium Fresenius to the patient.
The filter is for SINGLE USE only.

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper. **Heparin Sodium Fresenius** is given intravenously preferably by continuous injection, or by deep subcutaneous injection. The subcutaneous doses of **Heparin Sodium Fresenius** commonly used for prophylaxis (often termed "low dose") do not require monitoring.

The usual practice is to give an initial intravenous injection of 12 500 units of **Heparin Sodium Fresenius**, followed by doses of 10 000 units every 4 hours to keep the clotting time, tested not less than 3 hours after the last injection, at about 3 times the pre-treatment figure. The dose for this purpose usually ranges from 8 000 to 12 000 units. For continuous infusion 10 000 to 20 000 units of **Heparin Sodium Fresenius** is added to 1 litre of dextrose injection or sodium chloride 0,9 % injection and started at about 30 drops per minute.

A suggested initial dose for children is 50 units per kg body mass by intravenous infusion in dextrose injection 5 % increased to 100 units per kg every 4 hours to keep the clotting time at 20 to 30 minutes. If blood transfusions are required during anticoagulant therapy, 2 units of **Heparin Sodium Fresenius** per ml may be added to the transfused blood in addition to the dose already being administered. Bleeding from the site of operation is unlikely if **Heparin Sodium Fresenius** is started after the fourth postoperative day.

For treatment of venous thromboembolism: an intravenous loading dose of 5 000 units (10 000 may be required in severe pulmonary embolism) is followed by continuous intravenous infusion of 1 000 to 2 000 units/hour or subcutaneous injection of 15 000 units every 12 hours. Alternatively, intermittent intravenous dose of 5 000 to 10 000 units every 4 to 6 hours undiluted or diluted in 50 to 100 ml of dextrose 5 % in water or sodium chloride 0,9 % is suggested. Children and small adults are given a lower intravenous dose followed by maintenance with continuous infusion of 15 to 25 units/ kg per hour or subcutaneous injection of 250 units/kg every 12 hours.

For prophylaxis of postoperative venous thromboembolism: subcutaneous doses used are 5 000 units 2 hours before surgery then every 8 to 12 hours for 7 days or until the patient is ambulant. Similar doses are used to prevent thromboembolism during pregnancy in women with history of deep vein thrombosis or pulmonary embolism; the dose may need to be increased to 10 000 units every 12 hours during the third trimester.

SIDE EFFECTS

Blood and the lymphatic system disorders:

The following side effects have been reported and the frequencies are unknown:
Heparin Sodium Fresenius can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated.
Heparin-induced thrombocytopenia (HIT) and Heparin-induced thrombocytopenia and thrombosis (HITT) and delayed onset of HIT and HITT may occur.

Immune system disorders:

The following side effect has been reported and the frequency is unknown:
Hypersensitivity reactions may occur.

Skin and subcutaneous tissue disorders:

The following side effect has been reported and the frequency is unknown:
Skin necrosis and alopecia have occurred after prolonged use of **Heparin Sodium Fresenius**.

Musculoskeletal, connective tissue and bone disorders:

The following side effect has been reported and the frequency is unknown:
Osteoporosis resulting in spontaneous fractures has occurred after prolonged use of **Heparin Sodium Fresenius**.

General disorders and administration site conditions:

The following side effects have been reported and the frequencies are unknown:
Local irritant effects.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The main side effect of **Heparin Sodium Fresenius** is haemorrhage. Careful laboratory control is necessary. Bleeding may be encountered from an unsuspected lesion, such as a peptic ulcer. The haemorrhagic complications recorded include haematuria, haemarthrosis, wound haematoma and gastrointestinal bleeding. The haemorrhage may produce a haematoma in the surgical wound, but this is rarely serious if infection is prevented and large accumulations of blood are aspirated. Mild effects of heparin overdosage usually respond to simple withdrawal of **Heparin Sodium Fresenius**. In the event of major haemorrhage, the use of the specific heparin antagonist, protamine sulphate, is imperative.

IDENTIFICATION

A clear colourless or straw-coloured liquid in amber glass ampoules or vials, free from turbidity and from matter which deposits on standing.

PRESENTATION

1 ml amber glass ampoules packed with fillers in containers of 10.
5ml amber glass vials packed with filler in containers of 10.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Do not freeze.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

Heparin Sodium Fresenius 1 000 IU/1 ml (1 ml ampoule, 5 ml vial) J/8.2/405
Heparin Sodium Fresenius 5 000 IU/1 ml (1 ml ampoule, 5 ml vial) J/8.2/406
Heparin Sodium Fresenius 25 000 IU/1 ml (5 ml vial) J/8.2/407

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd
6 Gibaud Road
Korsten, 6020
Port Elizabeth
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT

discontinuation of **Heparin Sodium Fresenius**.
Priapism has been associated with **Heparin Sodium Fresenius** administration.
Dosage of **Heparin Sodium Fresenius** may need to be reduced in old people; elderly women appear to be especially susceptible to haemorrhage after **Heparin Sodium Fresenius** administration.

INTERACTIONS
Heparin Sodium Fresenius should be used with care in conjunction with oral anticoagulants or medicines like aspirin and dipyridamole, which effect platelet function. Non-Steroidal Anti-Inflammatory medicines may also increase the risk of haemorrhage. Other medicines which affect the coagulation process and which

Botswana:	1 000 iu/ml	BOT0600826 S4
	5 000 iu/ml	BOT0600836 S4
Namibia:	1 000 iu/ml	NS2 90/8.2/00411
	5 000 iu/ml	NS2 90/8.2/00413
	25 000 iu/ml	NS2 90/8.2/00412
Zimbabwe:	5 000 iu/ml	10.2 Anticoagulants 2011/10.2/4658: PP

12-142/04-15

SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORM

Heparin Sodium Fresenius 1 000 IU/1 ml
Heparin Sodium Fresenius 5 000 IU/1 ml
Heparin Sodium Fresenius 25 000 IU/1 ml

Injection

Read the entire leaflet carefully before you are given Heparin Sodium Fresenius
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **Heparin Sodium Fresenius** has been prescribed for you personally and you should not share your medicine with other people. It may harm them even if their symptoms are the same as yours.

WHAT HEPARIN SODIUM FRESENIUS CONTAINS
Each 1 ml amber glass ampoule or 5 ml amber glass vial contains heparin sodium (mucosal) dissolved in water for injection, where 1 ml of solution equates to 1 000 IU of heparin sodium (mucosal).
Each 1 ml amber glass ampoule or 5 ml amber glass vial contains heparin sodium (mucosal) dissolved in water for injection, where 1 ml of solution contains 5 000 IU of heparin sodium (mucosal).
Each 5 ml amber glass vial contains heparin sodium (mucosal) dissolved in water for injection, where 1 ml of solution contains 25 000 IU of heparin sodium (mucosal).
Chlorocresol has been used as a preservative. Heparin is obtained from porcine intestinal mucosa.

WHAT IS HEPARIN SODIUM FRESENIUS USED FOR
Heparin Sodium Fresenius belongs to a group of medicines known as anticoagulants. Anticoagulants work by decreasing the clotting ability of your blood and help stop clots forming in the blood vessels.
Heparin Sodium Fresenius injection is used for prevention and treatment of diseases caused by blood clots in your veins and/or arteries.

BEFORE YOU ARE ADMISTERED HEPARIN SODIUM FRESENIUS
You should not be administered Heparin Sodium Fresenius:
- if you have an allergy to heparin
- if you have, or may have, a tendency to bleed easily or a problem with your blood vessels
- if you have a low blood platelet count
- in conditions where bleeding is at particular risk for example:
  - o heart problems or high blood pressure
  - o blood disease or bleeding problems
  - o recent child birth
  - o threatened abortion
  - o liver disease
  - o kidney disease
  - o stomach ulcer
  - o surgery or wounds resulting in large open wounds
  - o prior to lumbar puncture (a procedure performed in order to collect a sample of spinal fluid) or regional anaesthetic block (local anaesthetic block)
  - o during or after eye, brain, or spinal cord surgery
  - o pulmonary tuberculosis (TB in the lung)

Special care should be taken with Heparin Sodium Fresenius
Tell your doctor or healthcare professional before being given the injection if:
- you are being treated for or undergoing treatment for lymphoblastic leukaemia (blood cancer) or
- renal dialysis.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before receiving Heparin Sodium Fresenius.
Heparin Sodium Fresenius does not cross the placenta and therefore adverse effects on the foetus would not be expected. Heparin has not been shown to cause birth defects or bleeding problems in the baby. However, use during the last three months of pregnancy or during the month following the baby's delivery, **Heparin Sodium Fresenius** may cause bleeding problems in the mother. Heparin does not pass into the breast milk.
Taking other medicines with Heparin Sodium Fresenius
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)
Some medicines and **Heparin Sodium Fresenius** may interfere with each other. These include:
- Medicines which effect blood clotting such as aspirin and warfarin, streptase and dipyridamole
- Medicines for hay fever such as antihistamines
- Non-Steroidal Anti-Inflammatory medicines for pain
- Penicillins and other types of antibiotics
- Medicines which cause increased volume of urine (diuretic)
- Potassium supplements such as potassium containing salt substitutes

HOW TO RECEIVE HEPARIN SODIUM FRESENIUS
Filter the solution prior to administering the medicine. The filter size must not be more than 20 µm.
You will not be expected to give yourself **Heparin Sodium Fresenius.** It will be given to you by a person who is qualified to do so.
Heparin Sodium Fresenius injection is usually given directly into your vein (intravenously) or under your skin at regular intervals and at a dose depending on the clotting time of your blood.
Heparin Sodium Fresenius can also be given by continuous infusion whereby the **Heparin Sodium Fresenius** is mixed with either a dextrose or 0,9 % sodium chloride solution and given by slow injection into your vein. (this is called an intravenous infusion).
Your doctor will decide what dose, how often and how long you will receive **Heparin Sodium Fresenius.** This depends on your condition and other factors, such as age, blood tests, method it is being given and whether or not other medicines are being given at the same time.
If you receive more Heparin Sodium Fresenius than you should
Since a healthcare professional will administer this medicine, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.
Symptoms that you need to be aware of in case of an overdose are :
- Nose bleeds
- Easy or unexplained bruising or bleeding
- Blood in your urine or stool

Tell your doctor if any of the above occure.

POSSIBLE SIDE EFFECTS
Heparin Sodium Fresenius can have side effects.
Not all side effects reported for **Heparin Sodium Fresenius** are included in this leaflet. Should your general health worsen or you experience any untoward effects while receiving **Heparin Sodium Fresenius**, please consult your doctor, pharmacist or other healthcare professional for advice.
Tell your doctor immediately if you experience any of the following reactions after receiving **Heparin Sodium Fresenius**.
- An allergic reaction (swelling of your lips, tongue, or face, difficulty in breathing, closing of your throat, or hives)
- Any prolonged or unexplained bleeding
- Pain, warmth, or redness in an arm or leg which could indicate a blood clot.

Tell your doctor as soon as possible if you experience any of the following reactions after receiving **Heparin Sodium Fresenius.**
- Irritation at the site of injection
- Hair loss
- Osteoporosis (following long term use) – a bone disease that leads to increased bone fractures
- Prolonged, painful erection

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF HEPARIN SODIUM FRESENIUS
Store all medicines out of reach of children.
Heparin Sodium Fresenius will be stored in the pharmacy or in the hospital wards at or below 25 °C.
Unused portions of the injection should be discarded.

PRESENTATION OF HEPARIN SODIUM FRESENIUS
The 1 ml amber glass ampoules packed with a filter in containers of 10.
The 5 ml amber glass vials packed with a filter in containers of 10.

IDENTIFICATION OF HEPARIN SODIUM FRESENIUS
The **Heparin Sodium Fresenius** injection is a clear colourless or straw-coloured liquid in amber glass ampoules or vials, free from turbidity and from matter which deposits on standing.

REGISTRATION NUMBERS
Heparin Sodium Fresenius 1 000 IU/ 1 ml (1 ml ampoule, 5 ml vial) Jl/8.2/405
Heparin Sodium Fresenius 5 000 IU/ 1 ml (1 ml ampoule, 5 ml vial) Jl/8.2/406
Heparin Sodium Fresenius 25 000 IU/ 1 ml (5 ml vial) Jl/8.2/407

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Fresenius Kabi Manufacturing SA (Pty) Ltd
6 Gibaud Road, Ronsten, 6020, Port Elizabeth, South Africa

DATE OF PUBLICATION
25 November 2011

Botswana:	1 000 iu/ml	BOT0600826 S4
	5 000 iu/ml	BOT0600836 S4
Namibia:	1 000 iu/ml	NS2 90/8.2/00411
	5 000 iu/ml	NS2 90/8.2/00413
	25 000 iu/ml	NS2 90/8.2/00412
Zimbabwe:	5 000 iu/ml	10.2 Anticoagulants 2011/10.2/4658: PP

12-142/04-15

Scheduling status S4

Proprietary name (and dosage form)

SPEC OXYTOCIN 10 I.U. Ampoule, SPEC OXYTOCIN 5 I.U. Ampoule

Composition
SPEC OXYTOCIN 10 is available in 1ml ampoules containing (16,66 µg/ml) synthetic oxytocin. Each 1ml ampoule contains 10 I.U. synthetic oxytocin.
SPEC OXYTOCIN 5 is available in 1ml ampoules containing (8,33 µg/ml) synthetic oxytocin. Each 1ml ampoule contains 5 I.U. synthetic oxytocin.
Pharmacological Classification A 19. Oxytocics.
Pharmacological action The active principle of oxytocin injection is a synthetic nonapeptide identical to oxytocin, a hormone released by the posterior lobe of the pituitary. Oxytocin exerts a stimulatory effect on the smooth musculature of the uterus, particularly towards the end of pregnancy, during labour, after delivery and in the puerperium, i.e. at times when the number of specific oxytocin receptors in the myometrium is increased. When given by low-dose intravenous infusion, oxytocin elicits rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour.
At higher infusion dosages, or when given as single injection, the substance is capable of causing sustained tetanic contractions.

Being synthetic, oxytocin does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like anti-diuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid intravenous bolus injection, consists in a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia.
Pharmacokinetics Where administered by intravenous or intramuscular injection for prevention or treatment of postpartum haemorrhage, oxytocin acts rapidly with a latency period of less than 1 minute by intravenous injection, and of 3 to 7 minutes by the intramuscular route. The oxytocic response lasts for 30 to 60 minutes after intramuscular administration; it may be shorter with intravenous injection.
When oxytocin is given by continuous intravenous infusion at doses appropriate for induction or enhancement of labour, the uterine response sets in gradually and reaches a steady state usually within 20 to 60 minutes. The corresponding plasma levels of oxytocin are comparable to those measured during spontaneous first-stage labour. Upon discontinuation of the infusion, or following a substantial reduction in the infusion rate, i.e. in the case of overstimulation, uterine activity declines rapidly, but may continue on an adequate lower level. The relative ease with which the rate and force of uterine contractions can be regulated by the intravenous infusion of oxytocin is due to the short half-life of oxytocin. Plasma protein-binding is very low. Removal of oxytocin from plasma is accomplished mainly by the liver and the kidneys. Less than 1 % of a given dose is excreted unchanged in the urine. The apparent volume of distribution is approximately 300 ml/kg in men and the metabolic clearance rate amounts to about 20 ml/kg per minute in men as well as in pregnant women. The extent to which oxytocin crosses the placenta or passes into breast milk is not known.
Indications
- Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy induced hypertension (pre-eclampsia).
- Enhancement of labour in selected cases of uterine inertia.
- During Caesarean section, following the delivery of the child.
- Prevention and treatment of postpartum haemorrhage and uterine atony.

Contra-indications
Hypersensitivity to the agent.
Hypertonic uterine contractions. Foetal distress. When delivery is not imminent. Any conditions in which for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated, e.g. significant cephalopelvic disproportion, foetal malpresentation, placenta praevia and vasa praevia, placental abruption, cord presentation or prolapse, overdistention or impaired resistance of the uterus to rupture as in multiple pregnancy, polyhydramnios, grand multiparity and in the presence of a uterine scar resulting from major surgery, including classical Caesarean section.
SPEC OXYTOCIN should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.
WARNINGS SPEC OXYTOCIN should not be given the same time as other oxytocics. (Also see "Precautions").
INTERACTIONS Prostaglandins may potentiate the uterotonic effect of SPEC OXYTOCIN and vice versa, therefore concomitant administration requires very careful monitoring.
Some inhalation anaesthetics, e.g. cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with SPEC OXYTOCIN has also been reported to cause cardiac rhythm disturbances. When given during or after caudal block anaesthesia, SPEC OXYTOCIN may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.
Pregnancy and Lactation Oxytocin causes uterine birth contractions and milk ejection during lactation.
Dosage and directions for use
• Induction or enhancement of labour.
SPEC OXYTOCIN should be administered as an intravenous drip infusion or preferably by means of a variable-speed infusion pump.
For drip infusion, it is recommended that 5 I.U. of SPEC OXYTOCIN be added to 500 ml of a physiologic electrolyte solution. For patients in whom infusion of sodium chloride must be avoided, 5 % dextrose solution may be used as the diluent (see "Precautions"). To ensure even mixing the bottle or bag must be turned upside-down several times before use. The initial infusion rate should be set at 1 to 4 milliunits (0,1 to 0,4 ml/min or 2 to 8 drops/min).
It may be gradually increased at intervals not shorter than 20 minutes until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10 milliunits/min (1 ml/min or 20 drops/min) and the recommended maximum rate is 20 milliunits/min (2 ml/minute = 40 drops per minute). In the unusual event that higher rates are required, as may occur in the management of foetal death in utero or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to SPEC OXYTOCIN, it is advisable to use a more concentrated SPEC OXYTOCIN solution e.g. 10 I.U. in 500 ml.
When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump. The frequency, strength and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine contractions is obtained, the infusion rate can be reduced.
The SPEC OXYTOCIN infusion should be discontinued immediately in the event of uterine hyperactivity or foetal distress. If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 I.U. SPEC OXYTOCIN, it is recommended that the attempt to induce labour should be ceased. It may be repeated on the following day starting again from a rate of 1 to 4 milliunits/min (0,1 to 0,4 ml/min or 2 to 8 drops/minute).
Inadvertent paravenous infusion of SPEC OXYTOCIN is not harmful.
Caesarean section: 5 I.U. intramurally immediately after delivery of the foetus.
• Prevention of postpartum uterine haemorrhage The usual dose is 5 I.U. slowly intravenously or 5 to 10 I.U. intramuscular after delivery of the placenta. In women given SPEC OXYTOCIN for induction of labour, the infusion rate should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.
• Treatment of postpartum uterine haemorrhage The usual dose is 5 to 10 I.U. i.m. followed in severe cases by intravenous infusion of a solution containing 5 to 20 I.U. of SPEC OXYTOCIN in 500 ml of a non-hydrating diluent, run at the rate necessary to control uterine atony.
• Incomplete, inevitable or missed abortion 5 I.U. slowly intravenous. If necessary followed by intravenous infusion at a rate of 20 to 40 milliunits/min or higher.
Side effects and special precautions
Side Effects
When SPEC OXYTOCIN is used by i.v. infusion for the induction or enhancement of labour, its administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hyperactivity, tetanic contractions or rupture of the uterus.
With either mode of administration (intramuscular or intravenous) SPEC OXYTOCIN may cause nausea, vomiting or cardiac arrhythmias. The table below contains adverse effects with possible, probable or unknown relationship to the use of oxytocin.

Organ System	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10 000, <1/1000)
Cardiovascular		Short-lasting hypotension accompanied by flushing and reflex tachycardia	Cardiac arrythmias	Anaphylactoid reaction resulting in shock
Gastro-intestinal disorders		Nausea,vomiting		
Blood and lymphatic disorder				Post-partum haemorrhage and fatal afibrinogenaemia due to obstetric complications
Respiratory		Dyspnoea		
Skin and appendages		Rash		

Others:
Prolonged or too rapid infusion of SPEC OXYTOCIN has an anti-diuretic effect, which may cause transient water intoxication. Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of SPEC OXYTOCIN together with large amounts of electrolyte free fluid were administered over a prolonged period of time (See "Precautions").
Pelvic haematomas, neonatal jaundice and retinal haemorrhage have been associated with the use of SPEC OXYTOCIN.
Rarely, maternal death from severe hypertension and subarachnoid haemorrhage has occurred.
Precautions
The induction of labour by means of SPEC OXYTOCIN should be attempted only when strictly indicated for medical reasons rather than for convenience. Administration should only be under hospital conditions and qualified medical supervision.
When given for induction and enhancement of labour, SPEC OXYTOCIN must only be administered as an intravenous infusion, and never by subcutaneous, intramuscular or intravenous bolus injection. Careful monitoring of foetal heart rate and uterine motility (frequency, strength and duration of contractions) is essential so that dosage may be adjusted to individual response. When SPEC OXYTOCIN is given for induction of labour, particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease and in patients above 35 years of age or with a history of lower-uterine-segment Caesarean section. Infusion volume should be low in patients with cardiovascular disorders. In the case of foetal death in utero and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism. Because SPEC OXYTOCIN possesses slight anti-diuretic activity, its prolonged intravenous administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage may cause water intoxication associated with hyponatraemia.
To avoid this rare complication, the following precautions must be observed whenever high doses of SPEC OXYTOCIN are administered over a long time: an electrolyte-containing diluent (must be used (not dextrose); the volume of infused fluid should be kept low by infusing SPEC OXYTOCIN at a higher concentration than recommended for the induction or enhancement of labour at term; fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.
When SPEC OXYTOCIN is used for prevention or treatment of uterine haemorrhage, rapid intravenous injection should be avoided, as it may cause an acute short-lasting drop in blood pressure.
Known symptoms of overdosage and particulars of its treatment
See "Side effects and Special Precautions". In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported. Overdosage following prolonged or too rapid infusion, may give rise to the following complications: foetal distress (bradycardia and arrhythmias), meconium staining of amniotic fluid, foetal asphyxia, Uterine hypertonicity, tetanic contraction, uterine rupture, extensive laceration of soft tissue, subarachnoid haemorrhage, severe hypotension, water retention and intoxication with convulsions, coma and even foetal and maternal death.
Treatment
When signs/symptoms of overdosage occur during continuous i.v. administration of SPEC OXYTOCIN, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance and control convulsions that may eventually occur by judicious use of diazepam.
Identification
SPEC OXYTOCIN 10 I.U. A clear, colourless solution, free from visible particles. **SPEC OXYTOCIN 5 I.U.** A clear, colourless solution, free from visible particles.
Presentation
SPEC OXYTOCIN 10 I.U. 1ml clear glass ampoule coded with single magenta-coloured ring on the neck of the ampoule.
Carton of 5 or 10 ampoules of 1 ml each.
SPEC OXYTOCIN 5 I.U. 1ml clear glass ampoules coded with two magenta-coloured rings on the neck of the ampoule. Carton of 5 or 10 ampoules of 1 ml each.
Storage instructions
Store in a refrigerator between 2 and 8 °C. Do not freeze. Do not remove the ampoule from the carton until required for use.
Protect from direct light. Discard any unused portion.
SPEC OXYTOCIN AMPOULES SHOULD BE KEPT OUT OF REACH OF CHILDREN.
Registration numbers:
SPEC OXYTOCIN 10 I.U.: A39/19/0074 Namibia: [S4] SPEC OXYTOCIN 10 I.U., Reg. No. 08/19/0108 Botswana: [S4] SPEC OXYTOCIN 10 I.U., Reg. No. B070701011 Zimbabwe: PP.SPEC OXYTOCIN 10,Reg.No. 2013/21.1.1/4804
SPEC OXYTOCIN 5 I.U.: 41/19/0303 Namibia: [S4] SPEC OXYTOCIN 5 I.U., Reg. No. 08/19/0107
Name and business address of the applicant
Specpharm (Pty) Ltd, cnr 13th Road and Pharmaceutical Road, Halfway House, Midrand, Gauteng
Date of publication of this package insert 10 August 2007

ALLIANCE

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

SYNTOMETRINE®
(Ampoule)

COMPOSITION:
Each 1 ml ampoule contains: 5 IU synthetic oxytocin and 0,5 mg ergometrine maleate. Glucose free.

PHARMACOLOGICAL CLASSIFICATION:
A:19 Oxytocics

PHARMACOLOGICAL ACTION:
SYNTOMETRINE® combines the rapid action of oxytocin with the sustained uterotonic effect of ergometrine.

INDICATIONS:
Active management of the third stage of labour.
Prevention and treatment of postpartum haemorrhage associated with uterine atony.

CONTRA-INDICATIONS:
Pregnancy, first stage of labour, second stage of labour before crowning of the head, primary or secondary uterine inertia, or a predisposition to uterine rupture as in patients of high parity or with a uterine scar from previous caesarean section. Impaired renal or hepatic function. Cases of severe toxaemia, Placenta praevia, mechanical obstruction to delivery, malposition of the foetus, or obvious foetal distress. Eclampsia; porphyria; sensitivity to any of the ingredients; hypertension; cardiac disease.

DOSAGE AND DIRECTIONS FOR USE:
Active management of third stage of labour: 1 ml SYNTOMETRINE® may be injected intramuscularly (but not intravenously), following crowning of the head, after delivery of the shoulder, or at the latest, immediately after delivery of the child. Expulsion of the placenta, which is normally separated by the first strong uterine contraction, should be assisted by gentle suprapubic pressure and controlled cord traction.

Prevention and treatment of postpartum haemorrhage: Following expulsion of the placenta, 1 ml intramuscularly, or intravenously if bleeding is heavy. Intravenous injections should be given slowly.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
There have been reports of nausea, vomiting and abdominal pain. Hypertension has occurred after rapid intravenous administration. Bronchospasm has been reported. Anaphylactic and other hypersensitivity reactions, cardiac arrhythmias and pelvic haematomas, and nausea and vomiting may occur.

There are reports of neonatal jaundice and retinal haemorrhage associated with the use of oxytocin in the management of labour.

SYNTOMETRINE® should not be given in breech presentation until after delivery of the child, and in multiple births, not until the last child has been delivered.

In postpartum haemorrhage, if bleeding is not arrested by the injection of SYNTOMETRINE®, the possibility of retained placental fragments should be excluded before a further injection is given.

Caution should be exercised in the presence of hypertension and septic conditions. Interaction with halothane has been considered to diminish the effect of ergometrine maleate on the uterus. Care is necessary in patients being treated with pressor agents, or who have received a vasoconstrictor in conjunction with local anaesthesia, as severe hypertension has been stated to occur. SYNTOMETRINE® should be given under full obstetric observation.

Intravenous injections should be given slowly to prevent bolus formation and hypertension.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Toxic effects are rare with oxytocin. Overdosage may give rise to uterine hypertonicity, tetanic contraction, uterine rupture, extensive laceration of soft tissue, severe hypertension, water retention and intoxication with convulsions and coma, foetal bradycardia, foetal arrhythmia, foetal asphyxia, foetal and also maternal death. Subarachnoid haemorrhage have occurred.

Overdosage of ergometrine maleate may give rise to gastrointestinal disturbances, hyper- or hypotension, respiratory depression, hypothermia and coma. The patient should be kept under close surveillance, fluid intake and output as well as electrolytes should be monitored.

IDENTIFICATION:
A clear, colourless solution with a faint bluish fluorescence in a 1 ml clear glass ampoule coded with two blue-coloured rings on the neck of the ampoule.

PRESENTATION:
Carton of 5 ampoules of 1 ml.

STORAGE INSTRUCTIONS:
Store in a refrigerator at 2 to 8 °C.

Do not freeze. Protect from light.

Do not remove from the outer container until required for use.

SYNTOMETRINE® AMPOULES SHOULD BE KEPT OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:
H/19/1966

NAME AND BUSINESS ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION:
Adcock Ingram Critical Care (Pty) Ltd, 1 Sabax Road, Aeroton, Johannesburg, 2013.

adcock ingram
critical care

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
Date approved by MCC: 30 March 2001
Last date amended: 26 Nov 2015

Novo Nordisk

Actrapid® HM (ge)

100 units/ml

Scheduling status:
S3

Proprietary name and dosage form:
Actrapid® HM (ge) (Injection)

Composition:
Each ml of the sterile aqueous solution contains 100 units of a sterile solution of genetically engineered monocomponent neutral insulin, preserved with 0,3% m-cresol.

Pharmacological classification:
A 21.1 Insulin preparations

Pharmacological action:

Pharmacodynamic properties
Actrapid® HM (ge) insulin is a fast acting soluble insulin.
Replaces the insufficiency of insulin secretion by the beta-cells of the pancreas.
The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells and simultaneously inhibit the output of glucose from the liver.
The effect of soluble insulin after subcutaneous administration begins after approximately ½ hour, reaches maximal effect between 1.5 and 3.5 hours and the entire duration of action is approximately 7 - 8 hours.

Pharmacokinetic properties
Insulin in the blood stream has a half life of a few minutes. Consequently the time action profile of an insulin preparation is determined solely by its absorption characteristics.
This process is influenced by several factors (e.g. insulin dosage, injection route and site).
The pharmacokinetics of insulins are therefore affected by significant intra- and interindividual variation.

Absorption
The maximum plasma concentration of soluble insulin is reached within 1.5 - 2.5 hours after subcutaneous administration.

Distribution
No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Indications:
Diabetes Mellitus

Contra-indications:
Hypoglycaemia
Hypersensitivity to human insulin or any of the excipients

Warnings:
Inadequate dosing or discontinuation of treatment may especially in Type 1 diabetes (insulin dependent diabetes mellitus), lead to hyperglycaemia.
The first symptoms of hyperglycaemia usually come on gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath.
In Type 1 diabetes, untreated hyperglycaemic events are potentially lethal.
Hypoglycaemia may occur if the insulin dose is too low in relation to the insulin requirement. Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.
Patients, whose blood glucose control is greatly improved by e.g. intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.
Transferring a patient to a new type or brand of insulin should be done under strict medical supervision.
Changes in strength, brand, type, species (animal, human, human insulin analogue) and/or method of manufacture may result in a change in dosage from that used with their usual insulin. If an adjustment is needed, it may be done with the first dose or during the first few weeks or months.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.
Before travelling between different time zones, the patient should be advised to consult the doctor, since this may mean that the patient has to take insulin and meals at different times.
Concomitant illness, especially infections and fever or conditions, usually increases the patient's insulin requirement.
Actrapid® HM (ge) is not recommended for use in infusion pumps for continuous subcutaneous insulin infusion due to the risk of precipitation in some pump catheters.

Interactions:
A number of medicines are known to interact with glucose metabolism.

The following substances may reduce the patient's insulin requirements:
Oral hypoglycaemic agents (OAHs), monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates and alcohol.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.
Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.
Octreotide/lanreotide may both decrease and increase insulin requirements.
Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Pregnancy and lactation:
There are no restrictions on the treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.
If untreated during pregnancy, diabetes mellitus constitutes a risk in intrauterine development. Diabetes therapy must therefore be continued during pregnancy.
Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and deaths in utero. Intensified blood glucose control and monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating a pregnancy.
Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy values.
There are no restrictions on the treatment of diabetes with Actrapid® HM (ge) during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However the dosage, diet or both may need to be adjusted.

Dosage and directions for use:
The dosage for each patient is individual and determined by his doctor in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual endogenous insulin production.
In patients with diabetes mellitus, optimized metabolic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.
Actrapid® HM (ge) is administered subcutaneously in the thigh or abdominal wall. If convenient the gluteal or deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.
Injection sites should be rotated within an anatomical region in order to avoid lipodystrophy. Injection into a lifted skin fold minimizes the risk of intramuscular injection. Keep the needle under the skin for at least 6 seconds to make sure the entire dose is injected.
Actrapid® HM (ge) may also be administered intravenously, which should only be carried out by health-care professionals.
Renal or hepatic impairment may reduce insulin requirement.

Injections using 10 ml vials and conventional syringes.
Clean the skin. Wipe the rubber disc on the vial with alcohol. Draw the piston of the syringe out to a distance corresponding to the quantity of insulin required. Gently agitate the vial of insulin. Then pierce the rubber disc with the needle, push the piston home, and turn the vial upside down. Draw the required amount of insulin into the syringe. Avoid air in the syringe and needle by working the piston slightly up and down. Make the injection at a suitable depth under the skin (subcutaneously). It is important that the injection is made with a syringe which is marked for use with an insulin preparation containing 100 units per ml. Failure to use the correct syringe, can lead to dosage errors.

Side effects and special precautions:
Side effects observed in patients using Actrapid® HM (ge) are mainly dose-dependent and due to the pharmacological effect of insulin. As for other insulin products, hypoglycaemia in general is the most frequent side effect. It may occur if the insulin dose is too high in relation to the insulin requirement.
In clinical trials and during marketed use, the frequency varies with the patient population and dose regimens therefore no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.
Frequencies of side effects from clinical trials, which by an overall judgment are considered related to Actrapid® HM (ge) are listed below. The frequencies are defined as: Uncommon (≥1/1,000, <1/100). Isolated spontaneous cases are presented as very rare, defined as: <1/10,000.

Immune system disorder
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
Symptoms of generalized hypersensitivity may include general skin rash, urticaria, sweating, gastrointestinal upset, and angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalized hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed "acute painful neuropathy" which is usually reversible.

Eye disorders
Very rare - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Uncommon - Diabetic retinopathy
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within the same area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Special Precautions
Effects on ability to drive and use machines:
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).
Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Known symptoms of overdosage and particulars of its treatment:
A specific overdose of insulin cannot be defined; however hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirements are administered.
- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or glucose given intravenously by a medical professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

Identification:
A colourless liquid free from turbidity and foreign matter.

Presentation:
Actrapid® HM (ge) vial: 10 ml vial made of glass (type 1). The vial is closed with a rubber closure and packed in a carton.
Snap-off cap:
The insulin vials are packed and shipped with a protective, colour coded, tamper-proof plastic cap. In order to withdraw insulin from a new vial, the cap must be removed. If the cap is not securely fastened to a newly purchased vial, return the vial to the pharmacy.

Storage instructions:
Do not freeze.
Keep out of sunlight.
Keep out of reach of children.
Insulin vials not in use to be stored between 2 °C and 8 °C (in a refrigerator).
Actrapid® HM (ge) vial in use may be kept at room temperature (max. 25 °C) for one month.
Note: Actrapid® HM (ge) should not be used if not water-clear and colourless.
Never use insulin after expiry date.

C: Digital Thermometer

TL8001B

Quick Details

Place of Origin: Guangdong, China (Mainland)	Brand Name: TLX	Model Number: TL8001B
	Usage: Household	Theory: Temperature Sensor
Measuring temperature range: -20 °c~70 °c (-58°F~158°F)	Measuring humidity range: 10%~99%TH	Accuracy: ±1°c(or ±2°F), ±5%RH
	Resolution: 0.1 °c(0.1°F)&1%RH	Display comfort level: comfort, wet or dry
Selectable temperature unit: C/F	Key feature: Max/Min memory	Dimensions: 110*100*20mm
Power supply: 1.5V	Net weight: 137g	

D: Supplementary Table

The accompanying factors that could affect the temperature fluctuations noted in Figure 10 of the Publishable manuscript are noted in Table I below.

Table I: Details of the greatest increase and greatest decrease in consecutive cold drug storage unit temperature measurements per day

Day of the Week	Temperature change	Fluctation ^{0}C	Change room temperature ^{0}C	Storage	Gel Packs	Number of Ampoules change	Time	Theatre number	Theatre in Use
Monday	Increase	8,1	-0,5	Plastic container	*2ABT to †1AB	0	11:00 -13:00	10	Y
	Decrease	-4,9	0,3	Plastic Container	2ABT	1	07:30 -09:00	10	Y
Tuesday	Increase	7,2	0,3	Cartoon/Plastic	2ABT	0	13:00 - 15:00	3	Y
	Decrease	-5,5	0,7	Cartoon/Plastic	1AB to 2ABT	1	11:00 -13:00	4	Y
Wednesday	Increase	1	0,5	Plastic container	2ABT	0	09:00 - 11:00	8	Y
	Decrease	-6,9	0,3	Plastic container	1AB to 2ABT	0	07:30 -09:00	8	N
Thursday	Increase	1,9	0	Plastic container	‡1SB	0	13:00 - 15:00	9	N
	Decreses	-2,6	0,5	Plastic container	1AB	4	07:30 - 09:00	5	Y
Friday	Increase	6	0,6	Plastic Container	2ABT to 1AB	1	07:30 - 09:00	10	N
	Decrease	-2,1	0,1	Plastic Container	2ABT	0	15:00 - 17:00	4	Y

*Two 15cm x 15 cm gel packs placed bottom and top of plastic container

† One 15cm x 15cm gel pack placed bottom of plastic container

‡ One 10cm x 10cm gel pack placed bottom of plastic container

E: Supplementary Figure

Each theatre was investigated for the number of measurements the cold drug storage unit was adequate to store all the anaesthetic refrigerated drugs for the week. Figure 1 illustrates the number of measurements that fulfilled manufacturer's recommended drug storage range of 2^0C – 8^0C, per theatre for a total of 30 cold drug storage unit temperature measurements taken in each theatre over the course of the week

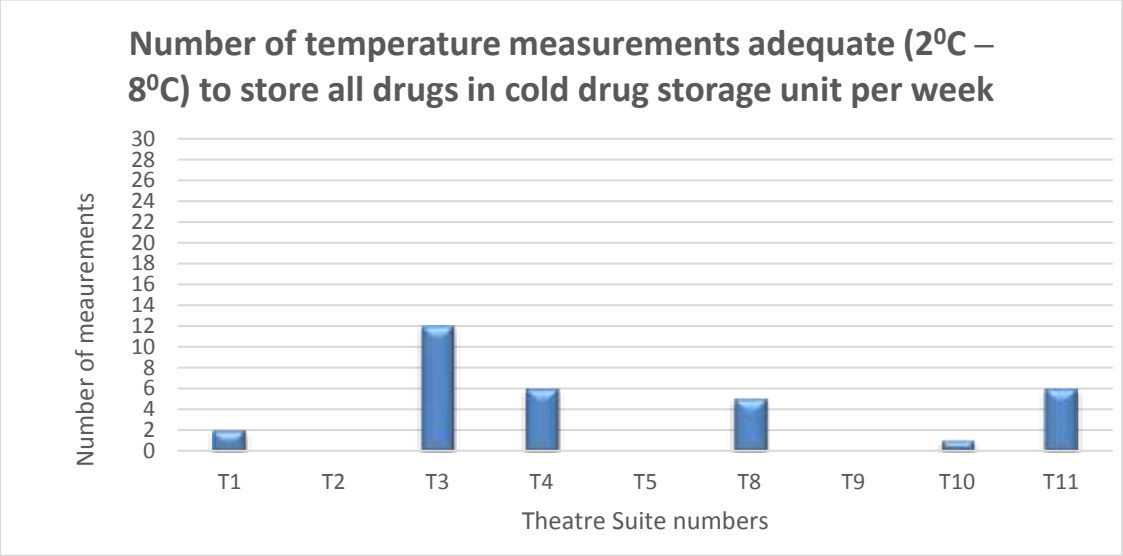


Figure 1: The number of measurements that fulfilled the manufactures' recommended temperature range of 2^0C – 8^0C, per theatre for the week

F: Letter of approval from HSREC

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YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

08-Oct-2018

Dear **Dr Nadia Cloete**

Ethics Clearance: **A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital**

Principal Investigator: **Dr Nadia Cloete**

Department: **Anaesthesiology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/0254/3010**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 0000624O; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

G: Letter of approval from HSREC after minor amendments

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

03-Oct-2019

Dear **Dr Nadia Cloete**

Ethics Number: UFS-HSD2018/0254/3010

Ethics Clearance: **A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital**

Principal Investigator: **Dr Nadia Cloete**

Department: **Anaesthesiology Department (Bloemfontein Campus)**

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

1. Theatre 6 and Theatre 7 (Cardiothoracic theatres) will not be included in the researcher's MMED research study
2. Placement of the temperature probe tip will be within the plastic container containing the refrigerated drugs

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
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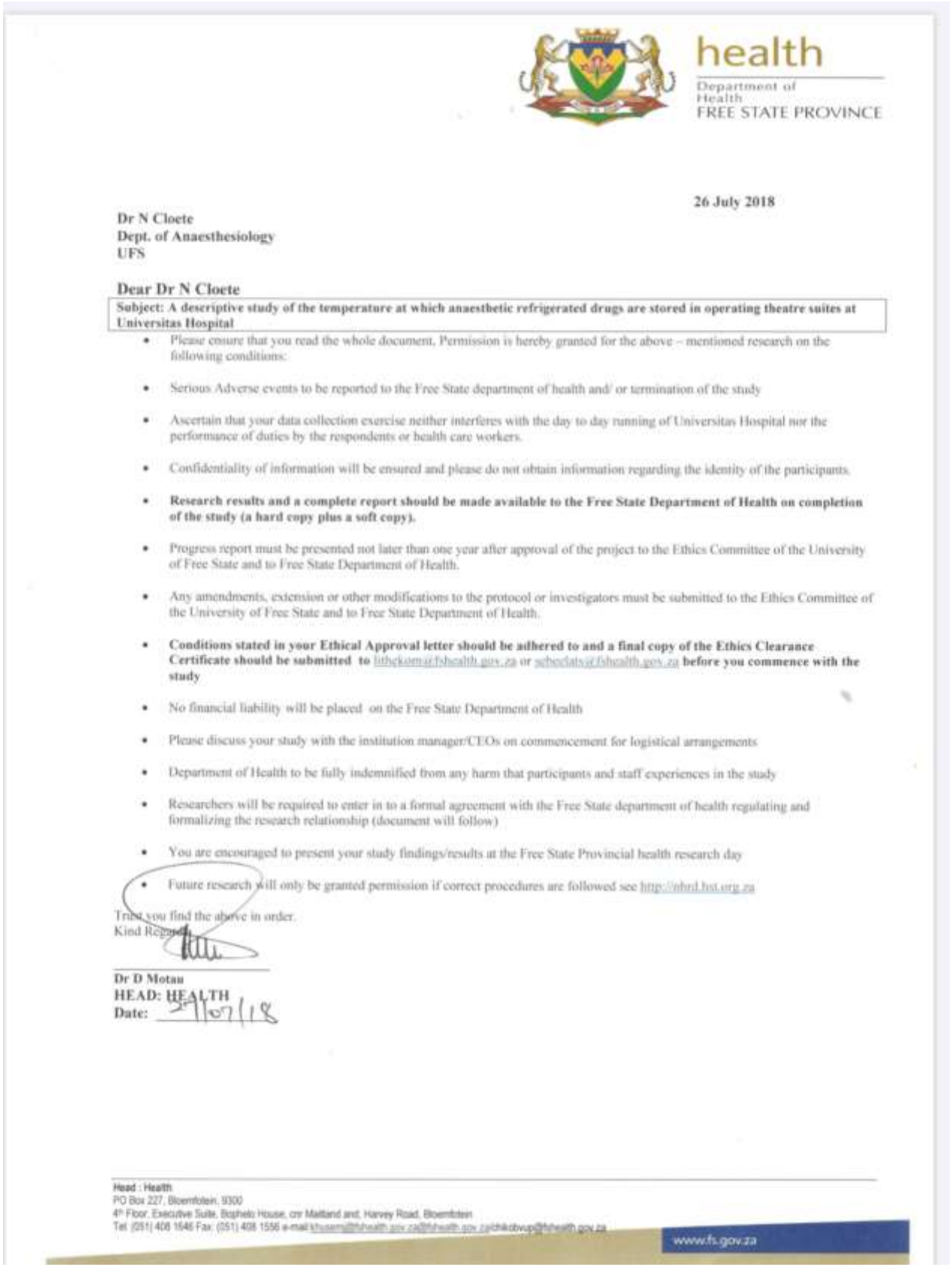
www.ufs.ac.za

H: Permission from Department of Health



health
Department of Health
FREE STATE PROVINCE

26 July 2018

Dr N Cloete
Dept. of Anaesthesiology
UFS

Dear Dr N Cloete

Subject: A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** lithekom@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 31/07/18

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1546 Fax: (051) 408 1556 e-mail khusem@fshealth.gov.za/@fshealth.gov.za/chikobwup@fshealth.gov.za

www.fs.gov.za

I: Permission letter from the Head of Department of Anaesthesiology

Department of Anaesthesiology
University of the Free State
Bloemfontein
10 April 2018

Prof G Lamacraft
Acting Head of Department Anaesthesiology
University of Free State
Bloemfontein

Re: Permission for research study

I, Nadia Cloete, am a registrar in Anaesthesiology at University of Free State. To ensure the completion of my training I plan to conduct an observational descriptive study to determine whether the temperatures in our cold drug storage unit in the theatre suites at Universities Hospital Theatre comply with manufacture storage temperature recommendations.

I hereby request permission to test the temperature of the cooler boxes housing refrigerator drugs in the theatre suite 1-11 during the day time theatre list at the following time: 07:30, 09:00, and 11:00, 13:00, 15:00 and 17:00 for five consecutive days.

No patient data will be required for my research and the data analysis will be done by the Department of Statistics, University of Free State.

Regards

Nadia Cloete
Registrar Anaesthesiology
University of the Free State

Dr P Van Zyl
Consultant Department of Pharmacology
University of the Free State

J: Permission letter from Theatre Manager

health
Department of Health
FREE STATE PROVINCE

Main Theatre
Universitas Hospital
11/09/2018

Dr Nadia Cloete

Re: Research study to be performed in theatre

I hereby grant you permission to carry on with your study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital

Yours truly

MP Seekoei (PNB4)
Assistant Manager

K: Research Protocol approved by the HSREC

MMed Research Protocol

Nadia Cloete

Anaesthesiology Registrar

University of Free State

UFS 2004008310

March 2018

A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital

15/04/2018

THE CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF THE FREE STATE

Dear Chair

Title: A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital

Enclosed please find the above research protocol for your evaluation and approval

Kind regards

Dr Nadia Cloete

Principal Investigator

Table of Contents

Title 4

Declaration of own work 4

Researchers 5

Summary of the Study (in lay man's terms) 6

Definitions 7

Introduction 8

Methodology 13

Pilot Study 17

Implementation of findings 19

Time schedule 20

Budget 21

Ethical Considerations 22

References 23

Appendices of the research protocol as approved by the Health Sciences Research Ethics Committee 24

Title

A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital

Declaration of own work

I, Nadia Cloete, hereby declare that the work for the following thesis with the title:

A descriptive study of the temperature at which anaesthetic refrigerated drugs are stored in operating theatre suites at Universitas Hospital

Was solely undertaken by myself and that no help was provided from other sources as those allowed. All relevant sections of this paper that use quotes or described an argument or concept developed by another author have been referenced to show that this material has been adopted to support my thesis.

Researchers

Principal Researcher

Dr Nadia Cloete

MB ChB (US), DA (SA)

Registrar in Anaesthesiology

Department of Anaesthesiology

University of Free State

UFS Student number: 2004008310

Cell number: 082 483 3637

Email: nadiagantana@gmail.com

Supervisor

Dr Paulina Maria van Zyl

MB ChB, MMedSc.(Clinical Pharmacology); Ph.D. (Clinical Pharmacology)

Senior Lecturer/ Clinical Pharmacologist

Department of Pharmacology

University of the Free State

UFS Staff number: 0789347

Contact number: 051 401 3096

Email: vzylpm@ufs.ac.za

Summary of the Study (in lay man's terms)

In each theatre suite it is imperative that drugs need to be stored in a manner that allows easy and quick access to the anaesthetist during procedures. This situation poses a problem for drugs that require storage below room temperature, according to manufacturer recommendations, as theatre suites are not equipped with a refrigerator. Storage of drugs in environments exceeding the recommended temperature have, according to drug degradation studies, led to physical and chemical breakdown.

To ensure easy accessibility to these "refrigerator drugs" the standard of practice is to remove them from a central refrigerator storage unit in the morning prior to commencing the first anaesthetic for the day and placing them in a temporary cold drug storage unit in each theatre suite. These units consist of a Styrofoam® cooler box with a frozen gel pack with a low melting point inside (Appendix A). The drugs are stored, either within a plastic container, loosely placed or in their original cartons, inside the cooler box (Appendix B).

The dilemma that arises with these cold drug storage units is that their temperature is neither displayed, recorded nor regulated. Although the cold drug storage unit ensures easy accessibility of refrigerator drugs to the anaesthetist, it could it be at the risk of hastening drug degradation due to incorrect storage conditions.

In this study, the researcher aims to measure the temperature in these cold drug storage units over the course of the day, on a number of days, to determine whether the cold drug storage unit complies with the drug manufacturer's storage temperature recommendations.

Definitions

Cold drug storage unit

This is a temporary cold storage unit consisting of a Styrofoam® cooler box. Inside the box is a frozen eutectic gel pack and placed on top of this gel pack are the refrigerator drugs, packaged in plastic container with a lid, in its original carton or loosely inserted. (Appendix A and Appendix B)

Refrigerator Drugs

Medications, which according to the manufacturers' recommendation, should be stored at 2 to 8^0C. The refrigerator drugs commonly used in by the anaesthetist in theatre are the following: Suxamethonium, Rocuronium, Cis-Atracurium, Atracurium, Phenylephrine, Heparin, Insulin and Oxytocin (Appendix C)

Room temperature

Comfortable temperature range indoors, usually considered to be 20 to 25^OC

Stability

Capacity of a particular formulation, in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic, toxicological, protective and informational specifications. The extent to which a product remains, within specified limits, and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of manufacture.[1]

Degradation products

Degradation products are impurities resulting from chemical changes that can occur during drug manufacturing, storage and transportation in response to changes in light, temperature, pH and humidity. The presence of these can affect pharmaceutical safety.[2]

Introduction

The Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) have set out guidelines on best practice regarding the storage of drugs in Anaesthetic rooms[3]. These guidelines reiterate the importance of secure drug storage, the contribution it makes to patient safety and the recognition that even short delays in accessing drugs may result in adverse patient outcomes. The Australian and New Zealand College of Anaesthetists share this sentiment and have specified, amongst other drugs, the need for muscle relaxants (which require storage at 2-8^{0}C) to be immediately available in any anaesthetising location[4].

The above reasoning ensues that a standard of practice exists that allow for anaesthetic drugs to be within easy access to the anaesthetist within the theatre suite. This poses a challenge for refrigerator drugs - which in our setting gets stored in a cooler box with a eutectic gel pack in the theatre suite for the duration of theatre time (Appendix A). Unfortunately these containers are not temperature regulated and one can question whether these storage conditions are compliant with the manufacturers' storage recommendations to ensure the stability of the pharmaceutical products they contain.

Manufacturers determine the adequate temperature storage conditions for pharmaceutical products needed to maintain the efficacy and safety until expiration date. These conditions are based on results from stability testing under a range of temperatures and therefore it is important that storage conditions be in compliance with package labelling to prevent their degradation[5].

The degradation of drugs are caused by chemical reactions (e.g. hydrolysis due to water exposure, oxidation due to oxygen exposure) and physical reactions (e.g. alteration of particle size, disintegration of a suspension, absorption of water). Temperature is recognised as the most important dependable factor for these reactions and therefore if drugs are stored at conditions that exceed the recommended temperature it can lead to degradation and loss of potency [6, 7].

It is important to note that it is not only storage of drugs above recommended temperatures that is a risk factor for accelerated degradation and risk of failure or unpredictable therapeutic response but that storage in temperature below recommendation may lead to the denaturing of proteinaceous products. This poses a challenge in emergency situations requiring immediate drug administration by the anaesthetist [8].

The current standard of practice at our institution regarding the handling of refrigerator drugs and maintaining adequate storage are as follows. At 7am the anaesthetic nurse of a theatre suite (theatre 1 to 11) collects refrigerator drugs from a food grade commercial fridge where drugs are stored at 4^0C to 6^0C in the theatre medication stock room. The anaesthetic nurse places the drugs in a Styrofoam® cooler box with one eutectic gel pack which can be seen as the "annexe" to the controlled storage refrigerator (Appendix A). Styrofoam® is a plastic polystyrene, a non-metallic solid with low thermal conductivity making it a good thermal insulator[9]. The iced gel pack decreases the Styrofoam® cooler box's interior temperature and limits the heat that enters the cooler box. The manner of placement of the drugs within this Styrofoam® cooler box is not standardised – it is either placed in a plastic container, in the original carton or loosely placed (Appendix B).

This cold drug storage unit is placed on the anaesthetic drug trolley in each theatre suite and subsequently exposed to ambient theatre temperatures. The current practice requires return of drugs to the controlled temperature unit (refrigerator) at theatre medication stock room at the end of the theatre list and permits the reuse if the medication is unopened. The duration of use of a particular theatre determines the time the drugs are out of a controlled temperature environment; on average 5 to 10 hours per day. The lack of "annexe" temperature display, regulation and monitoring poses the risk for drugs being exposed to temperatures deviating from the manufacturers recommendations.

The current system of passive refrigeration in theatre suites needs to be examined to determine whether it complies with manufacturer recommendation of storage temperature for pharmaceuticals or whether it is a source or condition potentially contributing to drug degradation.

The measuring instrument that will be used in this study will be a digital thermometer with a temperature measuring range of -20^0C to 70^0C. This thermometer has the manufacturers' assurance of an accuracy of $\pm1^0$C with a recording of the minimum and maximum temperature it is exposed to. The thermometer has a digital display (that will be placed on the outside of the cold drug storage unit) and a 1.5m cord with the measuring probe (that will be placed in a standard position within the cooler box). This thermometer will be purchased from Lasec SA (Pty) Ltd with the stock code: H3THE006Z-000002. (Appendix D).

Nine (old text: Twelve identical) thermometers will be used – one attached to each theatre's cold drug storage unit and the temperature probe to the anaesthetic workstation will be used to monitor ambient theatre temperature (old text: one to measure the ambient theatre temperature). A

synchronization reading procedure (Appendix I) will be performed by the researcher, with all thermometers used in this research, prior to initiation of the pilot study.

Below is a list of commonly stored drugs in the cold drug storage unit in the theatre suite with the manufacturers' recommendation regarding storage conditions. (Appendix C)

Drug Name and Manufacturer	Pharmacological Classification	Manufacturer Recommended storage temperature	Additional Manufacturer instructions	Recommendation by other studies
Suxamethonium 50mg/ml (2ml ampoule) *Fresenius Kabi Bodene (Pty) Ltd*	Muscle Relaxant	2 – 8^{O}C	Protect from light	Room temperature for 4.8 months [10] Room temperature (light resistant) for 2.8 months[6]
Rocuronium 10mg/ml (5ml) ampoule) *MSD (Pty) Ltd*	Muscle Relaxant	2 – 8^{O}C	Maximum storage 12 weeks not exceeding 30 ^{O}C If out of cold storage not to return	
Atracurium 10mg/ml (2.5ml ampoule) *GlaxoSmithKline*	Muscle Relaxant	2 – 8^{O}C	Protect from light. Do not freeze	
Cis – Atracurium 2mg/ml (2.5mls ampoule) *GlaxoSmithKline*	Muscle Relaxant	2 – 8^{O}C	Protect from light. Do not freeze. Do not remove from outer carton till administration. Diluted solution can be stored at 5 -25 ^{O}C	Room temperature (light resistant) for 3.8 months[6]
Phenylephrine 10mg/ml (1ml ampoule)*Abbott*	Vasopressor	2 – 25^{o}C	Protect from light. Keep covered in carton till use	

Drug Name and Manufacturer	Pharmacological Classification	Manufacturer Recommended storage temperature	Additional Manufacturer instructions	Recommendation by other studies
Heparin 1000IU/ml 5000IU/ml (4ml vial) *Fresenius Kabi Manufacturing SA*	Anticoagulant	Below 25 ^{O}C	Do not freeze	
Oxytocin 10 IU/ml (1ml ampoule) *Specpharm*	Oxytocic	2 – 8^{O}C	Do not freeze Do not remove ampoule from carton until use. Protect from direct sunlight	-5 ^{0}C to -20 ^{0}C for 7 days[11]
Insulin 100u/ml (10ml vial) *Novo Nordisk A/S*	Hypoglycaemic agent	2 – 8^{O}C Room temperature (max 25^{O}C) for one month	Do not freeze. Keep out of sunlight	Room temperature 2 weeks[12]

Aim and Objectives of the Study

Aim:

To assess whether the current temperature storage of refrigerator drugs in operating theatre suites are compliant with the manufacturers' storage recommendations.

Objectives:

Primary Outcome

To measure the temperature in the cold drug storage unit used in theatre suites for the storage of drugs during daytime working hours.

Secondary Outcome

To assess compliance of the storage temperatures of the refrigerator drugs within the cold drug storage unit with the manufacturer's storage temperature recommendations.To assess whether additional variables such as; the number of drugampoules or vials in the cold drug storage unit, the packaging of drugs within the cooler box (in a plastic container, in their original cartons or loosely placed) hold any relationship or correlation with the change in temperature measured.

Methodology

A: Study Design

An observational descriptive study design

B: Study Population / Participants

Nine (old text:11) Cold drug storage units (Styrofoam® cooler box with eutectic gel pack at the base inside. On top of the gel pack would be the refrigerator drugs placed either loosely, in a plastic container are their original packaging within the cooler box.) Appendix A, Appendix B

Nine (old text: 11) Theatres suites at Universitas Hospital where the above cold drug storage units are kept.

Time frame

5 consecutive days: Monday, Tuesday, Wednesday, Thursday, Friday

6 times each day: 07:30, 09:00, 11:00, 13:00, 15:00, 17:00

Inclusion Criteria

Nine (old text: All 11) cold drug storage units at Universitas Hospital Main Theatre (Theatre 1-11) on Monday, Tuesday, Wednesday, Thursday and Friday, between 07:30 and 17:00

Exclusion Criteria

Cold drug storage units in Cardiothoracic theatre (Theatre 6 & Theatre 7)

All cold drug storage units at Universitas Hospital theatre (Theatre 1-11) between 17:00 and 07:30

Cold drugs storage units at Universitas Annex Theatre i.e. theatre rooms separate from the main theatre complex

C: Measurements

Measuring instruments

The cold drug storage units in theatre suites (Appendix A)

Styrofoam® cooler box with eutectic gel pack at the base inside. On top of the gel pack would be the refrigerator drugs placed either loosely, in a plastic container or their original packaging within the cooler box.

A digital thermometer (Appendix D)

Display:	On the outside of Styrofoam® cooler box.
Probe:	On the inside of the Styrofoam® cooler box, within the plastic container (old text: at half the height of the cooler box)
9 (old text 11) Thermometers:	9 (old text 11) to measurement temperature in the cold drug storage units and the temperature probe attached to the anaesthetic workstation to measure ambient theatre temperature (old text: 1 to measure ambient theatre temperature)

Measuring Procedure

Measurements will be taken over 5 consecutive days (Monday, Tuesday, Wednesday, Thursday, Friday) from 07:30 to 17:00 in theatre1-5 and 8-11 (old text: 1-11) by the researcher.

07:30: The ambient temperature of theatre1-5 and 8-11 (old text: theatre 1-11 will be recorded and noted on the data sheet (Appendix E)

Digital thermometers will be identically placed in each cold drug storage unit as described and left attached for the day.

The temperature of the cold drug storage unit will be measured

The researcher will then record the following on the data sheet:

- the way in which the drugs are placed within the cold drug storage unit; in a plastic container, in their original packaging or placed loosely
- the number of ampoules of each drug in the cold storage unit

Collection of all the temperature measurements in the theatre1-5 and 8-11 (old text: theatre1-11) will take 10-15min in total.

09:00 Repeat the following measurements:

- ambient theatre temperature, the temperature in the cold drug storage unit, the number of ampoules of each drug present

11:00 Repeat the following measurements:

- ambient theatre temperature, the temperature in the cold drug storage unit, the number of ampoules of each drug present

13:00 Repeat the following measurements:

- ambient theatre temperature, the temperature in the cold drug storage unit, the number of ampoules of each drug present

15:00 Repeat the following measurements

- ambient theatre temperature, the temperature in the cold drug storage unit, the number of ampoules of each drug present

17:00 Repeat the following measurements

- ambient theatre temperature, the temperature in the cold drug storage unit, the number of ampoules of each drug present
- Temperature of the stock room refrigerator when returning drugs to the medication stock room.

If theatre finishes prior to 17:00, the theatre staff will be requested to leave the cold drug storage unit within the theatre suite. The researcher will place a sign next to the cold drug storage unit in the morning as a reminder to the nursing staff (Appendix H). In this manner,

more temperature fluctuation trends can be recorded. The start and end of anaesthesia time for the day will be documented on the data sheet and the researcher will return the cold drug storage unit and its content to the main storage cool grade commercial refrigerator in the medication stock room. The researcher will remove the digital thermometer from the cold drug storage unit and reattach it the following morning between 07:15 and 07h30.

The recorded temperatures measurements will be collected on the data sheet attached (Appendix E) and then transferred to an Excel spreadsheet for analysis.

D: Methodological and measurement errors

Nursing staff practice might be affected due to the study done. This will try to be minimised as anaesthetic nursing staff will be asked not to tamper with the contents of the cold drug storage units once installed in the morning (from 07:30 – 17:00) besides when needing to remove or replace the drugs.

Temperature readings might be affected by the number of times the Styrofoam® cooler box and plastic container or carton is opened and whether the lid of either or both is placed securely to prevent excessive influx of heat. The manner in which drugs are packaged within the cold drug storage unit will be captured on the data sheet, but no specific documentation will be made regarding number of times the unit was opened.

Whether the drugs are placed in the plastic containers, or whether they are inserted in their paper cartons, and the number of drugs placed in each plastic containers might affect the temperature within the cold drug storage unit. As each theatre number of drug requirements differ the number of individual drugs (ampoules or vials) will be documented with each temperature reading (07:30 – 17:00). The number of ampoules documented will assist in deducing the volume of drugs in the cold drug storage unit.

As the researcher will be recording the temperature measurements on the data sheet it could lead to observational bias. This factor has been reduced by using standardized digital thermometers with accurate display that will allow recording of temperature easily without needing interpretation or rounding off of figures as in the case of a mercury thermometer being used. The measuring of ambient theatre temperature too will be done with a digital thermometer as currently temperature is measured with a probe attached to the anaesthetic machine to display a digital reading – this might be attached to the patient at the time of measurement therefore it would be conducive to have a separate thermometer to prevent interference with patient care and anaesthetic management

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Pilot Study

After ethics approval has been granted and this protocol accepted, the researcher intends on conducting a pilot study.

The reasons for conducting the pilot study are as follows:

- To identify potential problem areas and shortcomings in the protocol prior to implementing the full study
- To test the measuring instrument
- To test the data collection process
- To familiarise myself with the data entry, coding of items and the analysis

The pilot study will take place on a Monday in one theatre suite at Universitas Hospital Main theatre. The data collection will adhere to the procedure documented in 'Methodology' of this protocol from 07:30 till 17:00.

The measurements collected will be captured on the data sheet, transferred onto an Excel spreadsheet and presented to the Department of Biostatistics of the University of the Free State.

Analysis of Data

Analysis of the data collected will be done by the Department of Biostatistics of the University of the Free State

Descriptive statistics namely means and standard deviations or medians and percentiles will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. The analysis of the data collected will be done by the Department of Biostatistics of the University of the Free State.

Cornel Van Rooyen

Researcher: Biostatistics

Faculty Health Sciences

University of the Free State

Contact number: 051 401 3114

Email: VanRooyenFC@ufs.ac.za

Implementation of findings

The data and information collected will be used for submission as a mini-dissertation in partial fulfilment of the requirements for an M.Med in Anaesthesiology and if granted, an article publication.

The study will help to determine whether the temperature of the cold drug storage unit in theatre is adequate for storage of refrigerator drugs in theatre suites during day theatre lists (07:30 -17:00) as specified by the manufacturer.

If the temperature in the cold drug storage unit complies with manufacture storage recommendations, then the current system can be used as a standard of practice conducive to prevent hastening drug degradation secondary to incorrect temperature storage conditions outside of a monitored unit for day time storage.

If the temperature in the cold drug storage unit does not comply with manufacture recommendations for storage, the current standard of practice can be adapted as follows:

1. Replace eutectic gel pack at a certain time of the day (according to temperature trends collected)
2. Have a cold drug storage unit with a temperature display visible to the anaesthetist and anaesthetic assistant
3. Motivate the need for small refrigerator in each theatre suite

This research project can contribute to future studies to determine degradation and potency of each drug stored in a cold drug storage unit in the theatre suite.

Time schedule

Protocol to Ethics Committee: March 2018

Pilot study: May 2018

Data Collection: June 2018

Data Processing: July 2018

Article writing: August - September 2018

Submission: October 2018

Budget

After ethics approval has been granted and my protocol accepted, I (the principal researcher) will fund this research at my own expense.

Stationary Cost:

R 800

Digital thermometer:

Reason for purchase: To adequately measure temperature inside the cold drug storage unit and ambient theatre temperature.

Amount: R127.00 each

12 units in total
(11 for theatre 1 to theatre 11 and an additional thermometer to measure theatre temperature)
= R127 x 12 = R 1524 (VAT R213.36)

= Total including VAT R1737.36 (See attached Appendix D)

Total Cost:

R 2537.36

Ethical Considerations

This study protocol will be submitted to the Health Sciences Research Ethics Committee, University of the Free State. A progress report will be submitted biannually and a report on conclusion of the research with also be submitted to the Ethics Committee.

Permission for the research will be obtained from the Acting Head of Department of the Department of Anaesthesiology, Prof G Lamacraft (Appendix F); Acting assistant manager of Universitas theatre complex, Matron P Seekoei (Appendix G) and the Department of Health Research Committee.

As this is an observational descriptive study involving no patients, ethical considerations are minimal. However, if the temperatures within the cold drug storage unit in theatre suites exceed recommended temperatures the Matron of theatre will be informed so that preventative measures can be put in place in an attempt to mitigate this risk.

The data file will be stored by the researcher in the Department of Anaesthesia in the University of the Free State.

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Appendices of the research protocol as approved by the Health Sciences Research Ethics Committee

A. Cold drug storage unit
B. Drug placement inside the cold drug storage unit
C. Package insert for medications stored in Cold drug storage unit
D. Digital Thermometer
E. Data Capture Sheet
F. Permission Letter: Head of Department Anaesthesiology
G. Permission Letter: Matron Universitas Theatre Complex
H. Study Notice on Passive Refrigerator System
I. Synchronization Reading procedure

Appendix A: Cold drug storage unit and drug storage packaging

Appendix B: Drug placement inside the Cold drug storage unit

Appendix C: Package insert of the refrigerator drugs stored in the cold drug storage unit

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

Suxamethonium Chloride Fresenius 100 mg/2 ml

Injection

COMPOSITION

Each 2 ml ampoule contains:

Active ingredient

Suxamethonium chloride	100 mg

Inactive ingredients

Sodium hydroxide 10 %	qs
Nitrogen	qs
Water for injection	2 ml

PHARMACOLOGICAL CLASSIFICATION

A 17.1 Peripherally-acting muscle relaxants

PHARMACOLOGICAL ACTION

Suxamethonium chloride is a depolarising, neuromuscular blocking agent. The initial effect is to depolarise the membrane in the same manner as acetylcholine, but more persistently, which results in a brief period of firing, manifested by transient muscular fasciculation. This phase is succeeded shortly by neuromuscular paralysis, the mechanism and even the primary site of which are still uncertain and controversial.

INDICATIONS

- to facilitate endotracheal intubation, bronchoscopy and oesophagoscopy, in combination with general anaesthesia with respiratory support
- to obtain rapid, short-term muscle relaxation in various orthopaedic procedures, such as the correction of dislocations and the alignment of fractures, with respiratory support
- as an adjuvant in surgical anaesthesia to obtain relaxation of skeletal muscle, particularly of the abdominal wall, so that operative manipulations are facilitated.

CONTRAINDICATIONS

Patients with a history of hypersensitivity to suxamethonium chloride or to any of the components of **Suxamethonium Chloride Fresenius**.

Patients who have suffered burns, massive trauma, exhibit myotonia and muscular rigidity, hemiplegia, paraplegia, muscular denervation and muscular dystrophies.

A family history of malignant hyperthermia.

Patients with renal impairment with a raised plasma-potassium concentration, severe long-lasting sepsis and severe hyperkalaemia.

Patients with glaucoma, penetrating wounds of eye or while the globe is open, or after initial surgery in massively traumatised patients.

Patients who are known to have atypical pseudocholinesterase.

In patients with low serum-pseudocholinesterase concentrations such as may occur in liver disease, malnutrition, severe anaemia, cancer, collagen diseases, severe dehydration, severe infections, myocardial infarction, myxoedema, renal impairment and in persons exposed to organophosphate insecticides or weed killers.

In patients with advanced myasthenia gravis, neurological defects or phaeochromocytoma.

WARNINGS AND SPECIAL PRECAUTIONS

Suxamethonium Chloride Fresenius is contraindicated in patients with burns, massive trauma, renal impairment with a raised plasma-potassium concentration, severe lung-sepsis and severe hyperkalaemia.

It is not generally recommended in uraemic patients especially those with high serum-potassium concentrations.

Caution is required when **Suxamethonium Chloride Fresenius** is given to patients with cardiac or respiratory disease or to those that have shown hypersensitivity to any neuromuscular blocker.

Hypothermia may enhance the neuromuscular blocking effects of **Suxamethonium Chloride Fresenius** and an increase in body temperature may reduce them.

Children may be at special risk from cardiac arrest associated with hyperkalaemia.

Suxamethonium Chloride Fresenius should be used with caution in patients with reduced pseudocholinesterase activity as it may prolong suxamethonium paralysis.

There have been reports of prolonged neuromuscular blockade following the use of **Suxamethonium Chloride Fresenius** in patients receiving lithium.

A repeat dose of Suxamethonium Chloride Fresenius within a short time (of the initial dose) may precipitate a vagal cardiac arrest. A rapidly acting anticholinergic agent (atropine) should be administered.

Malignant hyperpyrexia may occur. **Suxamethonium Chloride Fresenius** is a trigger agent for this accelerated hypermetabolic syndrome. It occurs in subjects with musculoskeletal disorders and also in apparently healthy individuals who are genetically predisposed to this syndrome. The symptoms are an increased respiratory carbon dioxide output, tissue hypoxia, usually but not necessary an increasing body temperature with or without muscular hypertonicity, often fatal cardiovascular complications, severe acidosis, hyperkalaemia and haemoglobinuria or myoglobinuria. Immediate treatment is required. Administer dantrolene sodium intravenously and treat the symptoms.

INTERACTIONS

Many medicines may interact with **Suxamethonium Chloride Fresenius**.

The mechanism of action may be due to a direct effect on neuromuscular transmission or an alteration of enzyme activity.

Suxamethonium Chloride Fresenius may interact with the following substances to produce prolonged paralysis: some aminoglycoside or polypeptide antibiotics including gentamycin, tobramycin, amikacin, clindamycin, lincomycin, polymyxins, tetracyclines, magnesium sulphate, narcotic analgesics, quinidine, cyclophosphamide, cimetidine, metoclopramide, phenelzine, oestrogens, tamoxifen, nifedipine and verapamil.

Following reports of apnoea, caution has been advised when spirotnin and neuromuscular blockers such as **Suxamethonium Chloride Fresenius** are used concomitantly.

Intravenous use of **Suxamethonium Chloride Fresenius** may develop tachyphylaxis and phase II block when inhalation anaesthetics are used. Neuromuscular blockers such as **Suxamethonium Chloride Fresenius** are potentiated in a dose-dependent manner by inhalation anaesthetics, and the dose may need to be reduced depending on the anaesthetic used and its concentration.

Bradycardia due to **Suxamethonium Chloride Fresenius** may be enhanced by inhalation agents such as halothane.

Administration of **Suxamethonium Chloride Fresenius** before or after the use of non-polarising relaxants may cause a mixed block.

Procaine and cocaine may competitively enhance the neuromuscular blocking activity of **Suxamethonium Chloride Fresenius**. The depolarising effects of **Suxamethonium Chloride Fresenius** may also be enhanced by neostigmine and other anticholinesterases; it has been recommended that eye drops containing a long-acting anticholinesterase should be discontinued at least 2 weeks before the administration of **Suxamethonium Chloride Fresenius**.

The effects of digitalis may be enhanced by **Suxamethonium Chloride Fresenius**, leading to cardiac dysrhythmias.

There have been reports of prolonged neuromuscular blockade following the use of **Suxamethonium Chloride Fresenius** in patients receiving lithium (see "Warnings and Special precautions").

PREGNANCY AND LACTATION

The safety of **Suxamethonium Chloride Fresenius** has not been established in pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE

Atropine could be considered before administration of **Suxamethonium Chloride Fresenius** to prevent excessive bradycardia, bronchial secretion, or other muscarinic effects. The recommended dose is 1 – 2 mg/kg intravenously.

SIDE EFFECTS

Immune system disorders

Frequencies unknown:

Hypersensitivity reactions to **Suxamethonium Chloride Fresenius** have been reported and bronchospasm has occurred.

Nervous system disorders

Frequencies unknown:

Prolonged neuromuscular blockade and apnoea may occur in patients with low serum concentrations of pseudocholinesterase and in those with an atypical pseudocholinesterase. The same conditions could result when excessive amounts of **Suxamethonium Chloride Fresenius** accumulate at the neuromuscular junction, for example following high or repeated doses. The nature of the block may change to one with characteristics similar to competitive block. This is known as **phase I block**.

Eye disorders

Frequencies unknown:

Suxamethonium Chloride Fresenius may cause a transient rise in intra-ocular pressure.

Cardiac disorders

Frequencies unknown:

Stimulation of the vagus nerve and parasympathetic ganglia by **Suxamethonium Chloride Fresenius** may be followed by bradycardia, other dysrhythmias, and hypotension. This may be exacerbated by the raised plasma-potassium concentration. Cardiac arrest has been reported.

Tachycardia and an increase in blood pressure due to stimulation of sympathetic ganglia has also been reported. Tachyphylaxis may occur with repeated doses.

Respiratory, thoracic and mediastinal disorders

Frequencies unknown:

There may be some increase in bronchial secretions due to the muscarinic action of **Suxamethonium Chloride Fresenius**.

Prolonged apnoea occurs in patients with low serum concentrations of pseudocholinesterase and in those with an atypical pseudocholinesterase.

Gastrointestinal disorders

Frequencies unknown:

A transient rise in intra-gastric pressure may occur secondary to abdominal muscle fasciculation. There may be some increase in bowel movements and in gastric and salivary secretions due to the muscarinic action of **Suxamethonium Chloride Fresenius**. Salivary gland enlargement may occur.

Musculoskeletal, connective tissue and bone disorders

Frequencies unknown:

The administration of **Suxamethonium Chloride Fresenius** results in transient fasciculations during the onset of depolarising block. Rhabdomyolysis, myoglobinaemia and myoglobinuria have been reported and may be associated with muscle damage following fasciculations.

Muscular pain similar to that following strenuous exercise may occur in the immediate postoperative period, particularly in patients who are ambulant but it is not related to dosage or the degree of fasciculation.

Plasma cholinesterase concentrations also fall during pregnancy and the puerperium and therefore maternal paralysis may be mildly prolonged.

General disorders and administration site conditions

Frequencies unknown:

Depolarisation of skeletal muscle produces an immediate increase in plasma-potassium concentration and this can have serious consequences in some patients.

Direct release of histamine from mast cells occurs and flushing, skin rash, bronchospasm and shock have been reported.

Malignant hyperpyrexia (see "Warnings and Special precautions").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See above for symptoms.

Prolonged apnoea should be treated until spontaneous respiration is fully restored.

A synthetic cholinesterase may be given to remove **Suxamethonium Chloride Fresenius**. Neostigmine should not be used.

When the action of **Suxamethonium Chloride Fresenius** is prolonged, the myoneural block may cease to be depolarising in type and may acquire some features of the paralysis produced by non-depolarising muscle relaxant agent, i.e. dual block. In these cases controlled ventilation should be continued until spontaneous respiration is fully restored.

IDENTIFICATION

Clear solution in amber glass ampoules.

PRESENTATION

Packs of 10 x 2 ml ampoules.

STORAGE INSTRUCTIONS

Store in a refrigerator (2 - 8 °C).

Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

M/17.1/270

NAME AND BUSINESS ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION

SODENE (PTY) LIMITED trading as Intramed
6 Gilbaud Road
Korsten
Port Elizabeth
South Africa
6020

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Last approved: 25 November 2011

12-427/03-16

Prescription only Medicine (POM)

Botswana: BOT0800843, S2

Namibia N52, 00/17.1/00441

Zimbabwe: 1.3 Cholinesterase inhibitors and muscle relaxants used in anaesthesia 20/3/31.3/4118, PP

Kenya: 14388, POM

Tanzania: TAN06, 253 NOAA BOD, POM

Zambia: 254/028, POM

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

ESMERON®

50 mg = 5 ml

100 mg = 10 ml

ROCURONIUM BROMIDE

Solution for intravenous injection only

COMPOSITION

ESMERON 50 mg = 5 ml

Each 5 ml vial contains 50 mg rocuronium bromide

ESMERON 100 mg = 10 ml

Each 10 ml vial contains 100 mg rocuronium bromide

Inactive ingredients

Sodium acetate, sodium chloride, glacial acetic acid and water for injection

PHARMACOLOGICAL CLASSIFICATION

A 4.2.3 Peripherally acting muscle relaxants

PHARMACOLOGICAL ACTION

Pharmacodynamics

Rocuronium bromide is a non-depolarising neuromuscular blocking agent, it acts by competing for nicotinic cholinoceptors at the motor end plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The ED_{95} (dose required to produce 95 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0,3 mg/kg rocuronium bromide. The ED_{95} in infants is lower than in adults and children (0,25, 0,27 and 0,42 respectively).

The clinical duration (the duration until spontaneous recovery to 25 % of control twitch height) with 0,6 mg/kg rocuronium bromide is 30 to 40 minutes. The total duration (time until application to recovery to 90 % of control twitch height) is 50 minutes. This mean time of spontaneous recovery, after which response from 25 to 75 % (recovery index) after a bolus dose of 0,6 mg/kg rocuronium bromide, is 14 minutes.

With lower dosages of 0,2 to 0,45 mg/kg rocuronium bromide (1/3 to 1/2 ED_{95}), onset of action is slower and duration of action is shorter (15 to 35 minutes). With high doses of 0,9 mg/kg the clinical duration is 100 minutes.

Cardiovascular surgery

In patients scheduled for cardiovascular surgery, the most common cardiovascular changes during the onset of maximum block following 0,6 to 0,9 mg/kg rocuronium bromide are an increase in heart rate up to 5 %, and an increase in mean arterial blood pressure up to 16 % from the control values.

Special populations

Obese: onset time in infants and children at an intubation dose of 0,6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults.

Reversal of muscle relaxation

Adrenal steroid and cholinesterase inhibitors, neostigmine, pyridostigmine or edrophonium as reappearance of T1 or at the first signs of clinical recovery, antagonises the action of rocuronium bromide.

Pharmacokinetics

After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration-time course runs in three exponential phases. In normal adults, the mean (95 % CI) elimination half-life is 72 (68 to 80) minutes, the (apparent) volume of distribution at steady state constitutes 203 (188 to 214) ml/kg and plasma clearance is 3,7 (3,5 to 3,9) ml/kg/min.

The plasma clearance in geriatric patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged (to 28 minutes) and the mean plasma clearance is reduced by 1 ml/kg/min.

In elderly (3 months to 1 year), the apparent volume of distribution at steady state conditions is increased compared to adults and children (1 to 8 years). In older children (2 to 8 years), a trend is seen towards higher clearance and shorter elimination half-life (approximately 25 minutes) compared to adults, younger children and infants.

When administered as a continuous infusion to patients under mechanical ventilation for 24 hours or more, the mean steady-state half-life and the mean apparent volume of distribution at steady state are increased. A large between-patient variability is found in overall clinical studies, reduced in kidney and absent at hepatic organ failure and individual patient comparisons. In patients with multiple organ failure a mean (± 2SD) elimination half-life of 2,0 (± 1,3) hours, a (apparent) volume of distribution at steady state of 1,3 (± 0,8) l/kg and a plasma clearance of 2,1 (± 0,8) ml/kg/min were found.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40 % within 12 to 24 hours. After injection of a radio-labelled dose of rocuronium bromide, excretion of the radio-label is on average 40 % in urine and 40 % in faeces after 5 days. Approximately 90 % is recovered as the parent compound.

INDICATIONS

ESMERON is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. ESMERON is also indicated as an adjunct in the Intensive Care Unit to facilitate intubation and mechanical ventilation for up to 2 days in adults 18 to 65 years.

CONTRA-INDICATIONS

Hypersensitivity to rocuronium or to the excipients or to any of the excipients.

There is insufficient data to support recommendations for the use of ESMERON in neonates (0 to 1 month).

ESMERON is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to lack of data on safety and efficacy.

Safety in pregnancy and lactation has not been demonstrated (see "**PREGNANCY AND LACTATION**").

WARNINGS AND SPECIAL PRECAUTIONS

Anaphylactic and anaphylactoid reactions may occur. Precautions for treating such reactions should always be given, particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Histamine Release and Histaminoid Reactions

Since neuromuscular blocking agents are known to be capable of inducing histamine release (both locally at the site of injection and systemically), the possible occurrence of such undesirable reactions at the site of injection and/or gland-related histamine or lymphocytic histaminoid reactions should always be taken into consideration when administering these medicines.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0,3 to 0,9 mg/kg ESMERON.

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after the full recovery from the neuromuscular blocking action of ESMERON.

Since ESMERON causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with it. If a medically unacceptable spontaneous respiration is restored, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

Residual curarisation has been reported for ESMERON. In order to prevent complications resulting from residual curarisation, it is recommended to antagonise only after the patient has recovered sufficiently from neuromuscular block. Geriatric patients (65 years and older) may be at increased risk for residual neuromuscular block. Other factors which could cause residual curarisation after extubation are the post-operative phase (such as medicine interactions or patient conditions) should it also be considered. If not used as part of standard clinical practice, the use of a neuromuscular agent should be considered, especially in those cases where residual curarisation is more likely to occur.

For long-term use of ESMERON in the Intensive Care Unit, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help prevent possible prolongation of neuromuscular block and/or skeletal muscle it is strongly recommended that the minimum dose that produces adequate block be used throughout the use of ESMERON.

Patients should receive adequate anaesthesia and sedation. Furthermore, ESMERON should be administered by the intubating personnel only or under supervision of experienced doctors who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Myopathy after long-term administration of ESMERON in the Intensive Care Unit, in combination with corticosteroid therapy, has been reported. Therefore, for patients receiving both ESMERON and corticosteroids, it is advised that use of ESMERON should be restricted as much as possible.

If succinylcholine is used for intubation, the administration of ESMERON should be delayed until the patient has clinically recovered from the neuromuscular block induced by succinylcholine.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of ESMERON:

Hepatic and/or biliary tract disease and renal failure

[illegible]

Prolonged circulation time

[illegible]

Neuromuscular disease

[illegible]

Hypothermia

[illegible]

Obesity

ESMERON may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when administered on an actual body weight.

Burns

[illegible]

Conditions which may increase the effects of ESMERON:

Alkalosis (eg. after severe vomiting), dehydration and muscle atrophy, hypermagnesaemia, hypokalaemia, after massive transfusions, hypothermia, renal failure, acidosis, hypercapnoea, cachexia.

Since a reduction in distribution rate, attended by a delay in recirculation should therefore be considered when [illegible]

INTERACTIONS

The following medicines have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents.

Effect of other medicines on ESMERON:

Increased effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of ESMERON. The effect is reduced by adjustment with maintenance dosing (see "**DOSAGE AND DIRECTIONS FOR USE, Surgical Procedures, Maintenance dosing**"). However, if the ESMERON infusion is discontinued during [illegible]
- After multiple or short-term infusions (see "**DOSAGE AND DIRECTIONS FOR USE**");
- Long-term concomitant use of corticosteroids and ESMERON in the Intensive Care Unit may result in prolonged duration of neuromuscular blockade (see "**WARNINGS AND SPECIAL PRECAUTIONS**").

Other medicines

- **Antibiotics:** Some aminoglycosides, lincosamides and polymyxins potentiate neuromuscular blockade.

Diuretics, quinidine and its derivatives, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics, [illegible] potentiate neuromuscular blockade and the administration of phenytoin or β-blocking agents.

Rocuronium has been reported after post-operative administration of [illegible] (see "**WARNINGS AND SPECIAL PRECAUTIONS**").

Decreased effect

- Prior chronic administration of phenytoin or carbamazepine.
- In cases of severe thermoglycemic fluid accumulation and oedema and inflammation.

Variable effect

- Administration of other non-depolarising neuromuscular blocking agents in combination with ESMERON may produce [illegible] or potentiation of the neuromuscular block, depending on the order of administration and the recommended dosage of each agent.
- Suxamethonium given after the administration of ESMERON, may produce potentiation or antagonism of the neuromuscular blocking effect of ESMERON.

Effect of ESMERON on other medicines:

ESMERON can be used with histamine liberating anaesthetics and may result in a quicker onset of action of [illegible].

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been demonstrated.

Caesarean Section

In cases requiring emergency Caesarean section, ESMERON can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and adequate precautions (proper preparation, appropriate premedication and following current methods) are taken to prevent pulmonary aspiration of gastric content.

However, ESMERON, administered in doses of 0,6 mg/kg, may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in patients undergoing Caesarean section. ESMERON does not affect Apgar score, foetal muscle tone or cause respiratory depression.

From umbilical cord blood sampling it is apparent that only minimal quantities of rocuronium bromide are transferred, which does not lead to the observation of clinical adverse effects in the newborn.

Doses of 0,6 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0,6 mg/kg is recommended in the patient group.

Reversal of neuromuscular block, induced by neuromuscular blocking agents, may be inhibited or unsatisfactory in patients receiving magnesium salts for eclampsia of pregnancy, because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of ESMERON should be reduced and/or titrated to twitch response.

DOSAGE AND DIRECTIONS FOR USE

Dosage

ESMERON should only be administered by, or under supervision of, experienced doctors who are familiar with the action and use of these medicines.

The dosage of ESMERON should be individualised in each patient. The method of anaesthesia and the expected duration of surgery, the method of execution and the expected duration of neuromuscular block, the possible interactions with other medicines that are administered concurrently, and the condition of the patient should be taken into account when determining the dose.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Intubation and anaesthetics potentiate the neuromuscular blocking effects of ESMERON. Potentiation however, becomes clinically relevant in the case use of anaesthesia, when the suitable agents have reached the tissue concentrations required for intubation action. Consequently, adjustments with ESMERON should be made by administering smaller maintenance doses at least two-point-minimum or by using lower infusion rates of ESMERON during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see "**INTERACTIONS**").

An adult presents the following dosage recommendations are to be a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures, and for use in the Intensive Care Unit.

Surgical Procedures

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0,6 mg/kg ESMERON, after which adequate intubation conditions are established within 90 seconds.

A dose of 1 mg/kg ESMERON is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia. At this dose adequate intubation conditions are established within 60 seconds in nearly all patients.

Higher doses

Should there be reason for selection of larger doses in individual patients, initial doses up to 2 mg/kg ESMERON have been administered during surgery without adverse cardiovascular effects being noted. The use of these high doses are of [illegible] clinical necessity. For small time and do not exceed the duration of action (see "**PHARMACOLOGICAL ACTION, Pharmacodynamics**").

Maintenance dosing

The recommended maintenance dose is 0,10 mg/kg ESMERON. In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to 0,1 mg/kg ESMERON. The maintenance doses should be given as a bolus when twitch height has returned to 25 % of control twitch height, or when 3 to 5 responses to train-of-four stimulation are present (see "**PHARMACOLOGICAL ACTION, Pharmacodynamics**").

Administration of effective long-lasting maintenance doses of rocuronium bromide with repetitive maintenance dosing at the recommended level has been observed.

Continuous infusion

If ESMERON is administered by continuous infusion it is recommended to give a loading dose of 0,6 mg/kg ESMERON and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10 % of control twitch height and to maintain 1 to 2 responses to train-of-four stimulation. In adults under inhalational anaesthesia, the infusion rate required to maintain neuromuscular block at 90 % block ranges from 0,3 to 0,6 mg/kg/h and under intravenous anaesthesia the infusion rate ranges from 0,3 to 0,4 mg/kg/h. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric patients

For infants (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 16 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.

For continuous infusion in paediatrics the infusion needs, with exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children to whom intubation doses as for adults are recommended, and this should be adjusted to maintain twitch response at 10 % of control twitch height, or to maintain 1 to 2 responses to train-of-four stimulation during the procedure.

The experience with ESMERON in rapid sequence induction in paediatric patients is limited. ESMERON is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure

The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0,6 mg/kg ESMERON.

Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0,075 to 0,1 mg/kg ESMERON, and the recommended infusion rate is 0,3 to 0,4 mg/kg/h (see "**Continuous infusion**"). See "**WARNINGS AND SPECIAL PRECAUTIONS**".

Overweight and obese patients

When used to overweight or obese patients, dose based on patients with a body mass of 20 % or more above ideal body mass should be reduced taking into account an obese body weight.

Intensive Care Procedures

Tracheal intubation

For tracheal intubation, the same doses should be used as mentioned above under surgical procedures.

Bio-assistance dosing

The use of an initial loading dose of 0.5 mg/kg ESMERON is recommended, followed by a continuous infusion as soon as body height measures up to 12 % an open-surgical wound of 1 to 2 hours or more after these doses. Dosage should always be titrated to effect on the individual patient. The recommended initial values are used for the neuromuscular of a neuromuscular block of 90 to 95 %. 0.6 to 2 mg/kg to train of four stimulation or adult patients: + 0.2 to 0.6 mg/kg/h during the first hour of administration, which will need to be discontinued during the following 60 to 90 hours, according to evaluation of response. Thereafter, individual dose adjustments to which determine normal.

A range between patient variability are heavily influenced agents has been found, with mean time to effect and range of 90 to 95 mg/kg/h depending on culture and extent of surgical fluid shift, concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Safety and efficacy beyond 3 days has not been established.

Following administration of vecuronium the intensive Care Unit, the time to recovery of the train of four ratio to 0.7 depends on the level of block at the end of the infusion. After a short bolus dose for 30 hours or more the median (range) time between return of block at the end of the infusion. After a short bolus dose for 30 hours or more the median (range) time between return of T1 to normal four stimulation and recovery of the train of four ratio to 0.7 was approximately 13.01 to 5 hours in patients without multiple organ failure and 4.6 to 29.7 hours in patients with multiple organ failure.

Administration

ESMERON is administered intravenously either as a bolus injection or as a continuous infusion.

Compatibilities

Compatibility studies with the following infusions fluids have been performed. In a mixed concentrations of 0.8 mg/ml and 2 mg/ml ESMERON. Mixed dilution ethanol in the combination with 4.8 % NaCl, 2 % Dextrose, 4 % Dextrose in saline. Stable under four conditions, diluted diluent is and bicarbonate.

Diluted solution should begin immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

Incompatibilities

Physical incompatibility has been documented for ESMERON when admixed to solutions containing the following medicines: amphotericin, amobarbital, aminophylline, calcium chloride, diazepam, diazepam, etomidate, anti-emetics, frusemide, hydrocortisone sodium succinate, insulin, metaraminol, methylprednisolone, prednisolone sodium succinate, thiopentone, thiopentone and vancomycin. ESMERON is also incompatible with thiopental.

ESMERON must not be mixed with other medicinal products except those mentioned above.

If ESMERON is administered via the same infusion line that is also used for other medicines, it is important that this infusion line is adequately flushed (e.g. with 0.9 % NaCl) between administration of ESMERON and medicines, for which incompatibility with ESMERON has been demonstrated, or for which compatibility with ESMERON has not been established.

SIDE EFFECTS

The most commonly occurring adverse drug reactions include reaction site pain reactions, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance are anaphylactoid and anaphylactoid reactions and associated symptoms. See also for other experiences below.

The following side effects have been reported and the frequencies estimates are as follows: Uncommon/Rare (≥ 1/1000 to < 1/100) very rare (< 1/10 000)

Immune system disorders

Very rare: Hypersensitivity, anaphylactoid reaction, anaphylactoid reaction, anaphylactic shock, anaphylactoid shock (see "WARNINGS AND SPECIAL PRECAUTIONS")

Nervous system disorders

Very rare: Muscle paralysis

Cardiac disorders

Uncommon/Rare: Tachycardia

Vascular disorders

Uncommon/Rare: Hypotension

Very rare: Circulatory collapse and shock, flushing

Respiratory, thoracic and mediastinal disorders

Very rare: Bronchospasm

Skin and subcutaneous tissue disorders

Very rare: Any erythrotic problems, urticaria, rash, erythematous rash

Musculoskeletal and connective tissue disorders

Very rare: After long term use in the Intensive Care Unit muscular weakness and a few cases of tetraplegia have been reported (see "WARNINGS AND SPECIAL PRECAUTIONS").

General disorders and administration site conditions

Uncommon/Rare: Withdrawal reflex (cut, decreased resistance of tracheal vessels) response, after removal medicine effect (the specific response, recurrence side pain, injection site reaction)

Very rare: Facial oedema, malignant hyperthermia

Injury, poisoning and procedural complications

Uncommon/Rare: Prolonged neuromuscular block, followed recovery from anaesthesia

Very rare: Airway complications of anaesthesia

Anaphylaxis

Although very rare, severe anaphylactic reactions to ESMERON have been reported. Anaphylactic/anaphylactoid reactions are hypotension, cardiovascular collapse (e.g. hypotension, tachycardia, circulatory collapse shock) and occasionally changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, the necessary precautions should always be taken in anticipation thereof.

Recurarisation

See "WARNINGS AND SPECIAL PRECAUTIONS".

Prolonged neuromuscular block

The most frequent adverse reaction to ESMERON consists of an extension of the medicinally pharmacological action beyond the one planned required. This may cause that potential muscle weakness to produce and prolonged overdose muscle paralysis with respiratory insufficiency apnoea.

Myopathy

Myopathy has been reported in the Intensive Care Unit after the use of ESMERON in combination with corticosteroids (see "WARNINGS AND SPECIAL PRECAUTIONS").

Local injection site reactions

Pain on injection has been noticed in patients who underwent rapid sequence induction of anaesthesia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. At the onset of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase-inhibiting agent fails to reverse the neuromuscular effects of ESMERON, ventilation must be maintained until spontaneous breathing is restored. Repeated dosages of an acetylcholinesterase-inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, pulmonary loading to overdose and apnoea and exposure until a cumulative dose of 750 x ED_{95}, 1200 mg/kg was administered.

Further treatment is symptomatic and supportive.

IDENTIFICATION

ESMERON 50 mg = 5 ml: 5 ml vial containing a clear, colourless to faintly yellow, aqueous solution.
ESMERON 100 mg = 10 ml: 10 ml vial containing a clear, colourless to faintly yellow, aqueous solution.

PRESENTATION

ESMERON 50 mg = 5 ml: Cartons containing 10 x 5 ml clear, glass vials each of which contains 50 mg vecuronium bromide in aqueous solution.
ESMERON 100 mg = 10 ml: Cartons containing 10 x 10 ml clear, glass vials each of which contains 100 mg vecuronium bromide in aqueous solution.

STORAGE INSTRUCTIONS

Store at 2 to 8 °C.

ESMERON may be stored at a temperature not exceeding 30 °C, for a maximum period of 12 weeks. Once kept outside the refrigerator, the product may not be returned there.

After opening of the container the solution is chemically stable for 24 hours at room temperature. Since ESMERON does not contain a preservative, any unused solution should be discarded.

Keep out of reach of children.

REGISTRATION NUMBERS

ESMERON 50 mg = 5 ml: 20/17.2/0197
ESMERON 100 mg = 10 ml: 20/17.2/0198

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd
117 16th Road
Midrand, Waterfall
1685
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT

02 March 2012 (Revised: 05 July 2013)

Name & Dose	
Registration Number	20/17.2/0197
Scheduling Status	S4(C)

ESMERON-SMR-ENG-1113114

MSD

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4(C)

PROPRIETARY NAME AND DOSAGE FORM

ESMERON® 50 mg = 5 ml
ESMERON® 100 mg = 10 ml
Solution for injection in vials

Read all of this leaflet carefully before you are given ESMERON.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- ESMERON has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

1. WHAT ESMERON CONTAINS

The active substance is: Vecuronium bromide

Each vial ESMERON contains: 10 mg vecuronium bromide

The other ingredients are: Acetic acid, sodium acetate, sodium chloride and water for injection.

Each vial ESMERON contains 1.21 mg sodium. No preservative has been added.

2. WHAT ESMERON IS USED FOR

ESMERON is the name of a group of medicines called muscle relaxants.

When you have an operation or [illegible] ESMERON can also be given in the Intensive Care Unit to help your muscles be relaxed.

3. BEFORE YOU RECEIVE ESMERON

You should not receive ESMERON

If you are hypersensitive (allergic) to vecuronium, the bromide ion or any of the other ingredients of ESMERON.

If there is insufficient time to suppress the use of ESMERON in children, (the 1 month).

ESMERON is not recommended for the facilitation of mechanical ventilation in the intensive care unit in which not used elderly patients in the Intensive Care Unit (ICU).

The safety in pregnancy and lactation has not been demonstrated.

Special care should be taken with ESMERON

Tell your anaesthetist exactly by doctor before you receive ESMERON:

- If you are often ill, or muscle weakness.
- If you have had kidney, heart, liver or gall bladder diseases.
- If you have had diseases affecting muscles and muscles.
- If you have fluid retention (oedema).

Tell your anaesthetist if any of these apply to you.

Some conditions may influence the effects of ESMERON e.g.

- Low calcium levels in the blood.
- Low potassium levels in the blood.
- High magnesium levels in the blood.
- Low levels of proteins in the blood.
- Too much carbon dioxide in the blood.
- Loss of too much water from the body e.g. by being sick, diarrhoea or sweating.
- Deep breathing/reading by too little oxygen in the blood (alkalosis).
- Burns.
- Being very overweight (obesity).
- Very low body temperature (if you burned).

If you are suffering from any of these conditions your anaesthetist will take this into account when deciding on the correct dose of ESMERON for you.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding your baby, inform your doctor, anaesthetist or other healthcare professional.

Driving and using machinery

Your doctor will inform you when it is safe to drive and operate potentially dangerous machinery after you have been administered ESMERON.

Do not drive or use any tools or machines if you feel tired or sleepy from the treatment with ESMERON.

Using other medicines with ESMERON

If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of ESMERON with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice.

Medicines which increase the effect of ESMERON

- Certain medicines which are used to treat bacterial infections (antibiotics).
- Certain medicines for heart disease or increased blood pressure (water tablets, calcium blockers, beta-blockers and quinidine).
- Certain anti-inflammatory medicines (corticosteroids).
- Medicines for severe depression (lithium, tricyclic [imipramine]).
- Magnesium salts.
- Certain medicines used to treat malaria.

Medicines which decrease the effect of ESMERON

- Certain medicines for epilepsy.
- Carbamazepine and procainamide.
- Certain protozoan inhibitors and for glaucoma and pneumonia.

In addition, you may be given other medicines before or during surgery which can alter the effects of ESMERON. These include certain anaesthetics, other muscle relaxants, medicines such as phenytoin and medicines which reverse the effects of ESMERON.

ESMERON may make you can cause rhythms work more quickly. Your anaesthetist will make this into account when deciding the correct dose of ESMERON for you.

4. HOW ESMERON IS USED

Dosage

The doctor will determine the dose. You will be given ESMERON before and/or during a surgical procedure. During the procedure it will be checked whether ESMERON is still working. You may be given additional doses if they are needed.

Method and route of administration

ESMERON will be given to you by your anaesthetist. ESMERON is given intravenously (into the vein), either as single injections or as a continuous infusion (a drip).

If you receive more ESMERON than you should

As your anaesthetist will be aware of your condition, it is unlikely that you will be given too much ESMERON. However, if this happens your anaesthetist will keep you breathing artificially (on a ventilator) until you can breathe on your own. You will be kept asleep while this takes place.

If you have any further questions on the use of ESMERON, ask your doctor or anaesthetist.

5. POSSIBLE SIDE EFFECTS

ESMERON can have side effects. If these side effects occur while you are under anaesthetic, they will be taken and treated by your anaesthetist.

Uncommon side effects (up to 1 in 10 people given ESMERON are affected)

- The medicine is less effective, or not effective enough.
- The medicine works for longer than expected.
- Lowering of blood pressure.
- Increase in heart rate.
- Pain near the site of injection.

Very rare side effects (< 1 in 10 000 people given ESMERON are affected)

- Allergic (hypersensitivity) reactions (such as difficulty in breathing, collapse of circulation and shock).
- Wheezing of the chest.
- Muscle weakness.
- Swelling, a rash or redness of the skin.
- Sudden fever, rash (rapid heartbeat, rapid breathing and stiffness), pain and/or weakness in your muscles.

Not all side effects reported for ESMERON are included in this leaflet. Should your general health worsen while using this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.

6. STORAGE AND DISPOSING OF ESMERON

Keep all medicines out of reach and sight of children.

ESMERON is stored in the hospital. Store in the refrigerator at 2 to 8 °C.

ESMERON may be stored at a temperature not exceeding 30 °C, for a maximum period of 12 weeks. Once kept outside the refrigerator, the product may not be returned there. After opening of the container the solution is chemically stable for 24 hours at room temperature. Since ESMERON does not contain a preservative, any unused solution should be discarded.

Do not use ESMERON after the expiry date stated on the label.

Do not use ESMERON if you notice that the solution contains particles or is not clear.

7. PRESENTATION OF ESMERON

ESMERON 50 mg = 5 ml: Cartons containing 10 x 5 ml clear, glass vials each of which contains 50 mg vecuronium bromide in aqueous solution.
ESMERON 100 mg = 10 ml: Cartons containing 10 x 10 ml clear, glass vials each of which contains 100 mg vecuronium bromide in aqueous solution.

8. IDENTIFICATION OF ESMERON

ESMERON 50 mg = 5 ml: 5 ml vial containing a clear, colourless to faintly yellow, aqueous solution.
ESMERON 100 mg = 10 ml: 10 ml vial containing a clear, colourless to faintly yellow, aqueous solution.

9. REGISTRATION NUMBERS

ESMERON 50 mg = 5 ml: 20/17.2/0197
ESMERON 100 mg = 10 ml: 20/17.2/0198

10. NAME AND ADDRESS OF REGISTRATION HOLDER

MSD (Pty) Ltd
117 16th Road
Midrand, Waterfall
1685
South Africa
Tel. No.: 011 655 3000

11. DATE OF PUBLICATION

02 March 2012 (Revised: 05 July 2013)

ESMERON-SMR-ENG-1113114

TRACRIUM®

SCHEDULING STATUS: 1000000141588

S4

PROPRIETARY NAME AND DOSAGE FORM:
TRACRIUM® Injection 2,5 ml (solution for injection)
TRACRIUM® Injection 5,0 ml (solution for injection)
Excipients: benzene sulphonic acid and water for injections.

COMPOSITION:
Each ampoule of 2,5 ml contains 25 mg atracurium besylate.
Each ampoule of 5,0 ml contains 50 mg atracurium besylate.

PHARMACOLOGICAL CLASSIFICATION:
A 17.1 Peripherally-acting muscle relaxants

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
TRACRIUM is a selective, competitive (non-depolarising) neuromuscular blocking agent.

Pharmacokinetic properties:
TRACRIUM is degraded mainly by spontaneous non-enzymatic decomposition (Hofmann elimination) which occurs at body pH and temperature into inactive metabolites. The termination of the neuromuscular blocking action of TRACRIUM is not dependent on metabolism and excretion by the liver or kidneys. The duration of action is therefore unlikely to be affected by impaired renal, hepatic or circulatory function. Variations in the blood pH and body temperature of the patient within the pathological range may alter the duration of action of TRACRIUM. It is possible that some decomposition may occur by non-specific plasma esterases. Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of TRACRIUM proceeds unaffected. TRACRIUM has no effect on the intra-ocular pressure.
When administered to laboratory animals in high doses, laudanosine, a metabolite of atracurium, has been associated with transient hypotension and, in some species, cerebral excitatory effects. Although seizures have been seen in ICU patients receiving atracurium, a causal relationship to laudanosine has not been established (see WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS:
TRACRIUM is used in anaesthesia to relax skeletal muscles and to facilitate controlled ventilation. TRACRIUM is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

CONTRA-INDICATIONS:
Known hypersensitivity to atracurium besylate.

WARNINGS AND SPECIAL PRECAUTIONS:
TRACRIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES, BUT HAS NO EFFECT ON CONSCIOUSNESS. THEREFORE IT SHOULD BE ADMINISTERED ONLY WITH ADEQUATE ANAESTHESIA AND ONLY BY OR UNDER THE CLOSE SUPERVISION OF AN ANAESTHETIST AND ADEQUATE FACILITIES MUST BE AVAILABLE FOR ENDOTRACHEAL INTUBATION AND ARTIFICIAL VENTILATION.
MONITORING OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED DURING THE USE OF TRACRIUM IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.
The potential exists for histamine release in susceptible patients. Caution should be exercised in administering TRACRIUM to patients with a history suggestive of an increased sensitivity to the effects of histamine.
TRACRIUM should be used with caution in patients with myasthenia gravis, other neuromuscular diseases and severe electrolyte disorders in which potentiation of other non-depolarising agents has been noted.
Resistance to non-depolarising neuromuscular blocking agents may develop in burn patients. Increased doses of non-depolarising muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.
In limited clinical studies, in patients susceptible to

Where a small vein is selected as the injection site, TRACRIUM should be flushed through the vein with physiological saline after injection. Where other anaesthetic medicines are administered through the same in-dwelling needle or cannula as TRACRIUM, it is important that each medicine is flushed through with physiological saline.
The dosage range recommended for adults is 0,3 to 0,6 mg/kg depending on the duration of complete neuromuscular block (full block) required and will provide muscle relaxation for 15 to 35 minutes. Complete neuromuscular block (full block) can be prolonged with supplementary doses of 0,1 to 0,2 mg/kg as required. Successive supplementary dosing does not give rise to accumulation. Endotracheal intubation can usually be accomplished within 90 seconds from the intravenous injection of 0,5 to 0,6 mg/kg. The neuromuscular block produced by TRACRIUM can be rapidly reversed by standard doses of anti-cholinesterase agents such as neostigmine and edrophonium preceded or accompanied by atropine, with no evidence of recurarization. Recovery from the end of complete neuromuscular block (full block) without use of neostigmine occurs in about 35 minutes as measured by restoration of the tetanic response to 95 % of normal neuromuscular function.

Use in Infusion:
After an initial bolus dose of 0,3 to 0,6 mg/kg, TRACRIUM can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion at rates of 0,3 to 0,6 mg/kg/hr (0,005 to 0,01 mg/kg/minute). Accurate dosage administration of the infusion may be achieved using a syringe pump. TRACRIUM can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25-26 °C reduces the rate of inactivation, therefore full neuromuscular block may be maintained by approximately half the original infusion rate at these low temperatures. TRACRIUM is compatible with the following infusion solutions for the times stated below:

Infusion Solution	Period of Stability
Sodium Chloride Intravenous BP (0,9 % m/v)	24 hours
Glucose Intravenous BP (5 % m/v)	8 hours
Ringers Injection USP	8 hours
Sodium Chloride (0,18 % m/v) and Glucose (4 % m/v) Intravenous Infusion BP	8 hours
Compound Sodium Lactate Intravenous Infusion BP (Hartmann's Solution)	4 hours

When diluted in these solutions to give atracurium concentrations of 0,5 mg/ml to 0,9 mg/ml, infusions of TRACRIUM are stable in daylight at temperatures of up to 30 °C.

Dosage in children:
The dosage requirements in children aged one month and over are similar to those in adults on a mg/kg basis.

Dosage in Elderly and High risk Patients:
TRACRIUM may be used at standard dosage in elderly patients and in those with cardiac, respiratory, renal (including end-stage failure) or hepatic failure. In elderly patients it is recommended, however that the initial dose be at the lower end of the range and that it be administered slowly. Patients with clinically significant cardiovascular disease may be more susceptible to the effects of transient hypotension. In these patients slow intravenous injection in divided doses over a period of 1-2 minutes is recommended. TRACRIUM should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.

Long-term use in Intensive Care Units (ICU):
TRACRIUM has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the risk-benefit ratio of neuromuscular blockade must be considered. Available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that TRACRIUM infusion requirements may increase with prolonged administration in the ICU. The effects of haemodialysis, haemoperfusion and haemofiltration on plasma levels of atracurium and its metabolites are unknown.

SIDE EFFECTS:
TRACRIUM does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, TRACRIUM has no clinically significant

malignant hyperthermia, TRACRIUM has not triggered this syndrome.
TRACRIUM is hypotonic and must not be administered into the infusion line of a blood transfusion.

Intensive Care Unit (ICU) Patients:
There have been reports of seizures in ICU patients who have been receiving atracurium concurrently with several other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). A causal relationship to laudanosine has not been established. In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.
There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids. These events have been seen infrequently in association with TRACRIUM and a causal relationship has not been established.

INTERACTIONS:
The neuromuscular block produced by TRACRIUM may be increased by the concomitant use of inhalation anaesthetics such as halothane, isoflurane and enflurane.
The neuromuscular block produced by TRACRIUM may be increased by the concomitant use of:

- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- antiarrhythmic medicines: propranolol, calcium channel blockers, lignocaine, procainamide and quinidine
- diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide
- magnesium sulphate
- ketamine
- lithium salts
- ganglion blocking agents: trimetaphan, hexamine.

Certain medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to TRACRIUM would be consequent on such development. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmic medicines (procainamide, quinidine), antirheumatic medicines (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.
The onset of non-depolarising neuromuscular block is likely to be lengthened and the duration of block shortened in patients receiving chronic anticonvulsant therapy. The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with TRACRIUM may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of TRACRIUM administered.
Any synergistic effect may vary between different medicines combinations. A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarizing agents such as TRACRIUM, as this may result in a prolonged and complex block which can be difficult to reverse with anti-cholinesterase drugs.

PREGNANCY AND LACTATION:
Use in pregnancy and obstetrics:
Safety during the course of pregnancy has not been established. TRACRIUM is suitable for maintenance of muscle relaxation during Caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses. It is not known whether TRACRIUM is excreted into human milk.

DOSAGE AND DIRECTIONS FOR USE:
Use by Injection:
TRACRIUM is administered by intravenous injection. It must not be mixed with thiopentone or any alkaline agents as the high pH would cause inactivation of the TRACRIUM.

effects on heart rate in the recommended dosage range and it will not counteract the bradycardia produced by many anaesthetic agents and by vagal stimulation during surgery. There have been reports of skin flushing, instances of transient hypotension and bronchospasm, which may be due to histamine release. Anaphylactoid reactions have also been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Signs: Prolonged muscle paralysis and its consequences are the main signs of overdosage.
Treatment: It is essential to maintain a patent airway together with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. Recovery may be hastened by the administration of anti-cholinesterase agents accompanied by atropine or glycopyrrolate, once evidence of spontaneous recovery is present.

IDENTIFICATION:
2,5 ml and 5,0 ml ampoules containing a clear faint yellow solution for intravenous administration.

PRESENTATION:
Box of 5 x Ampoules of 2,5 ml.
Box of 5 x Ampoules of 5,0 ml.

STORAGE INSTRUCTIONS:
Keep out of reach of children.
Store at 2 to 8 °C. Do not freeze.
Protect from light.
Open ampoules of TRACRIUM should be discarded immediately after use.

REGISTRATION NUMBER:
TRACRIUM Injection 2,5 ml: R/17.1/209
TRACRIUM Injection 5,0 ml: R/17.1/210

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:
GlaxoSmithKline South Africa (Pty) Ltd
39 Hawkins Avenue
Epping Industria 1
7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:
27 August 1998

GDS-13

TRACRIUM is a registered trade mark of the **GSK** group of companies

Botswana

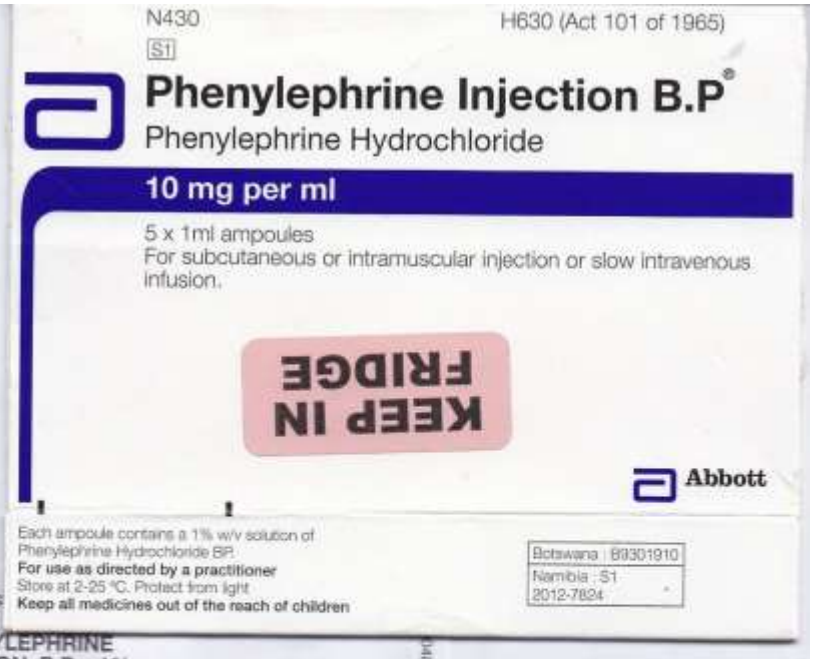
TRACRIUM® Injection 2,5 ml: Reg No. B9316845 S2
TRACRIUM® Injection 5,0 ml: Reg No. B9316850 S2

Namibia

TRACRIUM® Injection 2,5 ml: Reg No. 90/17.1/00585 NS2
TRACRIUM® Injection 5,0 ml: Reg No. 90/17.1/00586 NS2

Zimbabwe

TRACRIUM® Injection 2,5 ml: Reg No. 84/1.3/1848 PP
TRACRIUM® Injection 5,0 ml: Reg No. 84/1.3/1848 PP



For the Information of the Medical Profes

PHENYLEPHRINE INJECTION B.P. 1% 10 mg per ml

Phenylephrine Injection B.P. is a sterile solution of Phenylephrine Hydrochloride B.P. Phenylephrine Hydrochloride is a sympathomimetic amine with an action similar to that of noradrenaline, but with a greater duration of action and weaker pressor activity. It does not produce the adverse cardiac and central effects of adrenaline, and is less toxic. Phenylephrine is probably the safest of the vasoconstrictors to use with those anaesthetics which are liable to cause cardiac irregularities, and for this reason is used to combat hypotension during spinal anaesthesia. Since phenylephrine is not a central stimulant it does not cause the nervousness or apprehension often associated with the use of ephedrine or amphetamine. After injection phenylephrine produces peripheral vasoconstriction and an increase in arterial pressure; it also produces reflex bradycardia, an effect which is sometimes employed to arrest paroxysmal atrial tachycardia.

INDICATIONS

Phenylephrine Injection is indicated in the treatment of shock due to impaired vasomotor activity or following myocardial infarction. It is used to combat hypotension during spinal anaesthesia, or following sympathectomy or overdosage of hypotensive drugs (ganglion-blocking agents etc.) Phenylephrine is indicated in the treatment of paroxysmal atrial tachycardia.

CONTRA-INDICATIONS

Phenylephrine Injection is contra-indicated in the presence of severe hypertension, hyperthyroidism, partial heart-block, myocarditis, bradycardia, or seriously impaired coronary circulation. Depending upon the degree, senility may be a contra-indication to phenylephrine. It should not be given to patients being treated with a Monoamine Oxidase Inhibitor or within 2 weeks of stopping such treatment.

DOSAGE AND METHOD OF ADMINISTRATION

Dose:

By subcutaneous or intramuscular injection, Phenylephrine Injection equivalent to 5 mg of phenylephrine hydrochloiride. By intravenous injection, Phenylephrine Injection equivalent to 0.5 mg of phenylephrine hydrochloride. In the treatment of paroxysmal tachycardia phenylephrine may be administered intravenously as a 0.2% solution, the initial dose not exceeding 0.5 mg of phenylephrine and, depending upon the blood pressure response, subsequent doses not exceeding 0.2 mg. In peripheral vascular collapse phenylephrine may be given intramuscularly in a dose of 5 mg. Intravenously, phenylephrine can be given by the slow injection of 2.5 ml of a 0.02% solution. To combat hypotension during spinal anaesthesia the usual initial dose is 5 mg of phenylephrine by intramuscular or subcutaneous injection followed, if necessary, by supplementary doses of from 1 to 10 mg depending upon the response of the patient.

SIDE-EFFECTS

Phenylephrine Injection may cause a transient tingling and coolness of the skin and a temporary sensation of fullness in the head. Extravasation of the injection may occasionally cause local necrosis.

Further information is available on request.
PL/0014/5513

Botswana: B9301910
Namibia: S1
2012-7824

(Nov. '83)

Abbott

SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORM

Heparin Sodium Fresenius 1 000 IU/1 ml
Heparin Sodium Fresenius 5 000 IU/1 ml
Heparin Sodium Fresenius 25 000 IU/1 ml

Injection

COMPOSITION

1 ml ampoule and 5 ml vial containing 1 000 IU/1 ml heparin sodium (mucosal)
1 ml ampoule and 5 ml vial containing 5 000 IU/1 ml heparin sodium (mucosal)
5 ml vial containing 25 000 IU/1 ml heparin sodium (mucosal)
Heparin is obtained from porcine intestinal mucosa.

Inactive ingredients:
- Water for injections
- Preservative: Chlorocresol 0,1% *m/v*

PHARMACOLOGICAL CLASSIFICATION

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION

Heparin inhibits the clotting of blood both *in vitro*, and *in vivo*. Whole-blood clotting time, thrombin time and one-stage prothrombin time are prolonged, and thromboplastin generation is abnormal. Clotting time is proportional to the concentration of the medicine in the blood. However, with therapeutic doses bleeding time is usually unaffected and a patient can carry on normal activities, such as shaving, without danger of bleeding. The anticoagulant action of the heparin requires the presence of a plasma α-globulin, referred to as "heparin cofactor", a substance that appears to be identical with normal plasma antithrombin (antithrombin III). Heparin does not block prothrombin synthesis in the liver as do the oral anticoagulants but it does inhibit factors involved in the conversion of prothrombin to thrombin. This action is probably exerted by the facilitation of the formation of complexes of the heparin cofactor (antithrombin) with each of the four activated proteases of the coagulation cascade (activated factors IX, X, XI and XII). A similar heparin-stimulated reaction also occurs between antithrombin and thrombin. The detailed mechanism of this phenomenon may involve a heparin-induced conformational change of the inhibitor. It requires 30 to 40 times more heparin to inhibit the action of formed thrombin than it does to prevent thrombin formation. Therefore the prevention of thrombin formation is probably its primary effect. Heparin is not effective after oral or sublingual administration, but it is well absorbed after intramuscular or subcutaneous injection. In the blood it is evenly distributed between white cells and plasma. Heparin disappears exponentially from the circulation at a rate dependent upon the dose. The half-lives of 100, 200 and 400 units/kg, injected intravenously, are 56, 96 and 152 minutes respectively. Heparin is metabolized by the liver and a partially degraded, weakly active form of heparin (uroheparin) is excreted in the urine, after very large intravenous doses, up to 50 % of non-metabolised heparin may appear in the urine. The exact mechanism of renal elimination is unknown.

INDICATIONS

Heparin Sodium Fresenius is used as an anticoagulant in vascular surgery and occasionally in blood transfusions, but its chief use is in the treatment of arterial and venous thrombosis. It may also be used prophylactically after surgery to prevent thromboembolic complications.

CONTRAINDICATIONS

- Known hypersensitivity to heparin, especially when severe heparin-induced thrombocytopenia has occurred in recent months.
- Haemorrhagic blood disorders - especially thrombocytopenia and haemophilia. Haemorrhage, active or suspected - especially cerebrovascular, gastrointestinal, except in disseminated intravascular coagulation.
- Conditions where haemorrhage is a particular risk:
  - o Aneurysm, cerebral or aortic
  - o Hypertension severe or uncontrolled
  - o Threatened abortion
  - o Recent childbirth
- Subacute bacterial endocarditis
- Pericarditis
- Vasculitis, severe
- Active cavitating tuberculosis
- Visceral carcinoma if there is a possibility of intracranial metastasis
- Peptic ulceration
- During or after eye, brain or spinal cord surgery or trauma
- Prior to lumbar puncture or regional anaesthetic block
- Surgical or traumatic wounds resulting in large open surfaces
- Severe renal function impairment
- Severe hepatic function impairment
- Oesophageal varices

WARNINGS AND SPECIAL PRECAUTIONS

Filter the solution prior to administering the medicine. The filter size must not be more than 20 µm

Haemorrhage

Haemorrhage can occur at virtually any site in patients receiving **Heparin Sodium Fresenius**. An unexplained fall in haematocrit, fall in blood pressure or any other unexplained symptom should lead to serious consideration of a haemorrhagic event. Rarely retroperitoneal haemorrhage can occur even if the clotting time is not prolonged. **Heparin Sodium Fresenius** should be used with extreme caution in disease states in which there is increased danger of haemorrhage, e.g. some vascular purpuras, continuous tube drainage of the stomach or small intestine, menstruation.

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving **Heparin Sodium Fresenius** with a reported incidence of 0 to 30 %. Platelet counts should be obtained at baseline and periodically during **Heparin Sodium Fresenius** administration. Mild thrombocytopenia (count greater than 100 000/mm³) may remain stable or reverse even if **Heparin Sodium Fresenius** is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100 000/mm³ or if recurrent thrombosis develops (see Heparin-induced thrombocytopenia and Heparin-induced thrombocytopenia and thrombosis), the **Heparin Sodium Fresenius** should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin-induced thrombocytopenia (HIT) and Heparin-induced thrombocytopenia and thrombosis (HITT)

Heparin-induced thrombocytopenia (HIT) and Heparin-induced thrombocytopenia and thrombosis (HITT) may occur. Heparin-induced thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets.

HIT may progress to the development of venous and arterial thrombosis, a condition referred to as Heparin-induced thrombocytopenia and thrombosis (HITT). Thrombotic events may also be the initial presentation for HIT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischaemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100 000/mm³ or if recurrent thrombosis develops, the **Heparin Sodium Fresenius** should be promptly discontinued and alternative anticoagulants considered if patients require continued anticoagulation.

Since **Heparin Sodium Fresenius** has caused thrombocytopenia with severe thromboembolic complications, platelet counts should be monitored in patients receiving **Heparin Sodium Fresenius** for more than a few days.

Delayed onset of HIT and HITT

Heparin-induced thrombocytopenia and Heparin-induced thrombocytopenia and thrombosis can occur up to several weeks after the discontinuation of **Heparin Sodium Fresenius** therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of **Heparin Sodium Fresenius** should be evaluated for HIT and HITT.

General

A test dose has been recommended for patients with a history of allergy.

Heparin Sodium Fresenius inhibits the secretion of aldosterone which may cause hyperkalaemia. Plasma potassium levels should be monitored in those patients who are susceptible to hyperkalaemia, especially when receiving **Heparin Sodium Fresenius** for more than 7 days. The problem is normally resolved with the

may therefore increase the risk of haemorrhage include dextrans, thrombolytic enzymes such as streptokinase, high doses of penicillins, some cephalosporins, some contrast media, asparaginase and epoprostenol. Estimations of oral anticoagulant control may be modified by the action of **Heparin Sodium Fresenius** on prothrombin.

Heparin Sodium Fresenius has been reported incompatible with alteplase, amikacin sulphate, amiodarone hydrochloride, ampicillin sodium, aprotinin, benzylpenicillin, cefalotin sodium, ciprofloxacin lactate, cytarabine, dacarbazine, daunorubicin hydrochloride, diazepam, dobutamine hydrochloride, doxorubicin hydrochloride, droperidol, erythromycin lactobionate, gentamicin sulphate, haloperidol lactate, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulphate, meticillin sodium, netilmicin sulphate, some opiod analgesics, oxytetracycline hydrochloride, some phenothiazines, polymyxin B sulphate, streptomycin sulphate, tetracycline hydrochloride, tobramycin sulphate, vancomycin hydrochloride and vinblastine sulphate. **Heparin Sodium Fresenius** has also been reported to be incompatible with cisatracurium besilate, labetalol hydrochloride, levofloxacin, nicardipine hydrochloride, reteplase and vinorelbine tartrate. Although visually compatible cefmetazole sodium is reported to inactivate heparin sodium.

PREGNANCY AND LACTATION

Heparin Sodium Fresenius does not cross the placenta and therefore adverse effects on the foetus would not be expected. **Heparin Sodium Fresenius** is considered safer to the foetus than warfarin when used during pregnancy. **Heparin Sodium Fresenius** has not been shown to cause birth defects or bleeding problems in the baby. However, use during the last three months of pregnancy or during the month following baby's delivery may cause bleeding problems in the mother.

Heparin does not pass into the breast milk.

DOSAGE AND DIRECTIONS FOR USE

Filter the solution prior to administering the medicine. The filter size must not be more than 20 µm.
Draw up Heparin Sodium Fresenius from the ampoule or vial using the filter provided. Do not use this filter for the administration of Heparin Sodium Fresenius to the patient.
After withdrawal of Heparin Sodium Fresenius from the ampoule or vial, remove the filter and discard appropriately.
Administer Heparin Sodium Fresenius as per prescription using a NEW needle. Do not use filter needle to administer Heparin Sodium Fresenius to the patient.
The filter is for SINGLE USE only.

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper. **Heparin Sodium Fresenius** is given intravenously, preferably by continuous injection, or by deep subcutaneous injection. The subcutaneous doses of **Heparin Sodium Fresenius** commonly used for prophylaxis (often termed "low dose") do not require monitoring.

The usual practice is to give an initial intravenous injection of 12 500 units of **Heparin Sodium Fresenius**, followed by doses of 10 000 units every 4 hours to keep the clotting time, tested not less than 3 hours after the last injection, at about 3 times the pre-treatment figure. The dose for this purpose usually ranges from 6 000 to 12 000 units. For continuous infusion 10 000 to 20 000 units of **Heparin Sodium Fresenius** is added to 1 litre of dextrose injection or sodium chloride 0,9 % injection and started at about 20 drops per minute.

A suggested initial dose for children is 50 units per kg body mass by intravenous infusion in dextrose injection 5 % increased to 100 units per kg every 4 hours to keep the clotting time at 20 to 30 minutes. If blood transfusions are required during anticoagulant therapy, 3 units of **Heparin Sodium Fresenius** per ml may be added to the transfused blood in addition to the dose already being administered. Bleeding from the site of operation is unlikely if **Heparin Sodium Fresenius** is started after the fourth postoperative day.

For treatment of venous thromboembolism: an intravenous loading dose of 5 000 units (10 000 may be required in severe pulmonary embolism) is followed by continuous intravenous infusion of 1 000 to 2 000 units/hour or subcutaneous injection of 15 000 units every 12 hours. Alternatively, intermittent intravenous dose of 5 000 to 10 000 units every 4 to 6 hours undiluted or diluted in 50 to 100 ml of dextrose 5 % in water or sodium chloride 0,9 % is suggested. Children and small adults are given a lower intravenous dose followed by maintenance with continuous infusion of 15 to 25 units/ kg per hour or subcutaneous injection of 250 units/kg every 12 hours.

For prophylaxis of postoperative venous thromboembolism: subcutaneous doses used are 5 000 units 2 hours before surgery then every 8 to 12 hours for 7 days or until the patient is ambulant. Similar doses are used to prevent thromboembolism during pregnancy in women with history of deep vein thrombosis or pulmonary embolism; the dose may need to be increased to 10 000 units every 12 hours during the third trimester.

SIDE EFFECTS

Blood and the lymphatic system disorders:
The following side effects have been reported and the frequencies are unknown:
Heparin Sodium Fresenius can give rise to haemorrhage as a consequence of its action. It can also cause thrombocytopenia, either through a direct effect or through an immune effect producing a platelet-aggregating antibody. Consequent platelet aggregation and thrombosis may therefore exacerbate the condition being treated.
Heparin-induced thrombocytopenia (HIT) and Heparin-induced thrombocytopenia and thrombosis (HITT) and delayed onset of HIT and HITT may occur.

Immune system disorders:
The following side effect has been reported and the frequency is unknown:
Hypersensitivity reactions may occur.

Skin and subcutaneous tissue disorders:
The following side effect has been reported and the frequency is unknown:
Skin necroses and alopecia have occurred after prolonged use of **Heparin Sodium Fresenius**.

Musculoskeletal, connective tissue and bone disorders:
The following side effect has been reported and the frequency is unknown:
Osteoporosis resulting in spontaneous fractures has occurred after prolonged use of **Heparin Sodium Fresenius**.

General disorders and administration site conditions:
The following side effects have been reported and the frequencies are unknown:
Local irritant effects.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The main side effect of **Heparin Sodium Fresenius** is haemorrhage. Careful laboratory control is necessary. Bleeding may be encountered from an unsuspected lesion, such as a peptic ulcer. The haemorrhagic complications recorded include haematuria, haemarthrosis, wound haematoma and gastrointestinal bleeding. The haemorrhage may produce a haematoma in the surgical wound, but this is rarely serious if infection is prevented and larger accumulations of blood are aspirated. Mild effects of heparin overdosage usually respond to simple withdrawal of **Heparin Sodium Fresenius**. In the event of major haemorrhage, the use of the specific heparin antagonist, protamine sulphate, is imperative.

IDENTIFICATION

A clear colourless or straw-coloured liquid in amber glass ampoules or vials, free from turbidity and from matter which deposits on standing.

PRESENTATION

1 ml amber glass ampoules packed with filters in containers of 10.
5ml amber glass vials packed with filter in containers of 10.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Do not freeze.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

Heparin Sodium Fresenius 1 000 IU/1 ml (1 ml ampoule, 5 ml vial) J/8.2/405
Heparin Sodium Fresenius 5 000 IU/1 ml (1 ml ampoule, 5 ml vial) J/8.2/406
Heparin Sodium Fresenius 25 000 IU/1 ml (5 ml vial) J/8.2/407

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd
6 Gibaud Road
Korsten, 6026
Port Elizabeth
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT

26 November 2012

discontinuation of **Heparin Sodium Fresenius**.
Priapism has been associated with **Heparin Sodium Fresenius** administration.
Dosage of **Heparin Sodium Fresenius** may need to be reduced in old people; elderly women appear to be especially susceptible to haemorrhage after **Heparin Sodium Fresenius** administration.

INTERACTIONS
Heparin Sodium Fresenius should be used with care in conjunction with oral anticoagulants or medicines like aspirin and dipyridamole, which effect platelet function. Non-Steroidal Anti-Inflammatory medicines may also increase the risk of haemorrhage. Other medicines which affect the coagulation process and which

Botswana:	1 000 iu/ml	BOT0600826, S2
	5 000 iu/ml	BOT0600836, S2
Namibia:	1 000 iu/ml	NS2 90/8.2/00411
	5 000 iu/ml	NS2 90/8.2/00413
	25 000 iu/ml	NS2 90/8.2/00412
Zimbabwe:	5 000 iu/ml	10.2 Anticoagulants 2011/10.2/4858, PP

12-142/04-15

SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORM

Heparin Sodium Fresenius 1 000 IU/1 ml
Heparin Sodium Fresenius 5 000 IU/1 ml
Heparin Sodium Fresenius 25 000 IU/1 ml

Injection

Read the entire leaflet carefully before you are given Heparin Sodium Fresenius
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **Heparin Sodium Fresenius** has been prescribed for you personally and you should not share your medicine with other people. It may harm them even if their symptoms are the same as yours.

WHAT HEPARIN SODIUM FRESENIUS CONTAINS
Each 1 ml amber glass ampoule or 5 ml amber glass vial contains heparin sodium (mucosal) dissolved in water for injection, where 1 ml of solution equates to 1 000 IU of heparin sodium (mucosal).
Each 1 ml amber glass ampoule or 5 ml amber glass vial contains heparin sodium (mucosal) dissolved in water for injection, where 1 ml of solution contains 5 000 IU of heparin sodium (mucosal).
Each 5 ml amber glass vial contains heparin sodium (mucosal) dissolved in water for injection, where 1 ml of solution contains 25 000 IU of heparin sodium (mucosal).
Chlorocresol has been used as a preservative. Heparin is obtained from porcine intestinal mucosa.

WHAT IS HEPARIN SODIUM FRESENIUS USED FOR
Heparin Sodium Fresenius belongs to a group of medicines known as anticoagulants. Anticoagulants work by decreasing the clotting ability of your blood and help stop clots forming in the blood vessels.
Heparin Sodium Fresenius injection is used for prevention and treatment of diseases caused by blood clots in your veins and/or arteries.

BEFORE YOU ARE ADMINISTERED HEPARIN SODIUM FRESENIUS
You should not be administered Heparin Sodium Fresenius:
- if you have an allergy to heparin
- if you have, or may have, a tendency to bleed easily or a problem with your blood vessels
- if you have a low blood platelet count
- in conditions where bleeding is at particular risk for example:
  - o heart problems or high blood pressure
  - o blood disease or bleeding problems
  - o recent child birth
  - o threatened abortion
  - o liver disease
  - o kidney disease
  - o stomach ulcer
  - o surgery or wounds resulting in large open wounds
  - o prior to lumbar puncture (a procedure performed in order to collect a sample of spinal fluid) or regional anaesthetic block (local anaesthetic block)
  - o during or after eye, brain, or spinal cord surgery
  - o pulmonary tuberculosis (TB in the lung)

Special care should be taken with Heparin Sodium Fresenius
Tell your doctor or healthcare professional before being given the injection if:
- you are being treated for or undergoing treatment for lymphoblastic leukaemia (blood cancer) or
- renal dialysis.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before receiving Heparin Sodium Fresenius.
Heparin Sodium Fresenius does not cross the placenta and therefore adverse effects on the foetus would not be expected. Heparin has not been shown to cause birth defects or bleeding problems in the baby. However, use during the last three months of pregnancy or during the month following the baby's delivery, **Heparin Sodium Fresenius** may cause bleeding problems in the mother. Heparin does not pass into the breast milk.
Taking other medicines with Heparin Sodium Fresenius
Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)
Some medicines and **Heparin Sodium Fresenius** may interfere with each other. These include:
- Medicine which affect blood clotting such as aspirin and warfarin, sitepiase and dipyridamole
- Medicines for hay fever such as antihistamines
- Non-Steroidal Anti-Inflammatory medicines for pain
- Penicillins and other types of antibiotics
- Medicines which cause increased volume of urine (diuretic)
- Potassium supplements such as potassium containing salt substitutes

HOW TO RECEIVE HEPARIN SODIUM FRESENIUS
Filter the solution prior to administering the medicine. The filter size must not be more than 20 µm.
You will not be expected to give yourself **Heparin Sodium Fresenius**. It will be given to you by a person who is qualified to do so.
Heparin Sodium Fresenius injection is usually given directly into your vein (intravenously) or under your skin at regular intervals and at a dose depending on the clotting time of your blood.
Heparin Sodium Fresenius can also be given by continuous infusion whereby the **Heparin Sodium Fresenius** is mixed with either a dextrose or 0,9 % sodium chloride solution and given by slow injection into your vein (this is called an intravenous infusion).
Your doctor will decide what dose, how often and how long you will receive **Heparin Sodium Fresenius**. This depends on your condition and other factors, such as age, blood tests, method it is being given and whether or not other medicines are being given at the same time.
If you receive more Heparin Sodium Fresenius than you should
Since a healthcare professional will administer this medicine, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage. Symptoms that you need to be aware of in case of an overdose are -
- Nose bleeds
- Easy or unexplained bruising or bleeding
- Blood in your urine or stool

Tell your doctor if any of the above occurs.

POSSIBLE SIDE EFFECTS
Heparin Sodium Fresenius can have side effects.
Not all side effects reported for **Heparin Sodium Fresenius** are included in this leaflet. Should your general health worsen or you experience any untoward effects while receiving **Heparin Sodium Fresenius**, please consult your doctor, pharmacist or other healthcare professional for advice.
Tell your doctor immediately if you experience any of the following reactions after receiving **Heparin Sodium Fresenius**:
- An allergic reaction (swelling of your lips, tongue, or face, difficulty in breathing, closing of your throat, or hives)
- Any prolonged or unexplained bleeding
- Pain, warmth, or redness in an arm or leg which could indicate a blood clot.

Tell your doctor as soon as possible if you experience any of the following reactions after receiving **Heparin Sodium Fresenius**:
- Irritation at the site of injection
- Hair loss
- Osteoporosis (following long term use) – a bone disease that leads to increased bone fractures
- Prolonged, painful erection

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

STORING AND DISPOSING OF HEPARIN SODIUM FRESENIUS
Store all medicines out of reach of children.
Heparin Sodium Fresenius will be stored in the pharmacy or in the hospital wards at or below 25 °C.
Unused portions of the injection should be discarded.

PRESENTATION OF HEPARIN SODIUM FRESENIUS
The 1 ml amber glass ampoules packed with a filter in containers of 10.
The 5 ml amber glass vials packed with a filter in containers of 10.

IDENTIFICATION OF HEPARIN SODIUM FRESENIUS
The **Heparin Sodium Fresenius** injection is a clear colourless or straw-coloured liquid in amber glass ampoules or vials, free from turbidity and from matter which deposits on standing.

REGISTRATION NUMBERS
Heparin Sodium Fresenius 1 000 IU/ 1 ml (1 ml ampoule, 5 ml vial) J/8.2/405
Heparin Sodium Fresenius 5 000 IU/ 1 ml (1 ml ampoule, 5 ml vial) J/8.2/406
Heparin Sodium Fresenius 25 000 IU/ 1 ml (5 ml vial) J/8.2/407

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Fresenius Kabi Manufacturing SA (Pty) Ltd
6 Gibaud Road, Korsten, 6020, Port Elizabeth, South Africa

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Botswana:	1 000 iu/ml	BOT0600826, S2
	5 000 iu/ml	BOT0600836, S2
Namibia:	1 000 iu/ml	NS2 90/8.2/00411
	5 000 iu/ml	NS2 90/8.2/00413
	25 000 iu/ml	NS2 90/8.2/00412
Zimbabwe:	5 000 iu/ml	10.2 Anticoagulants 2011/10.2/4858, PP

12-142/04-15

NIMBEX®

10000000119098

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:
NIMBEX® 2 mg/ml (2,5 ml) Injection
NIMBEX® 2 mg/ml (5 ml) Injection
NIMBEX® 2 mg/ml (10 ml) Injection
NIMBEX® 5 Injection

COMPOSITION:
Each NIMBEX 2 mg/ml (2,5 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.
Each NIMBEX 2 mg/ml (5 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.
Each NIMBEX 2 mg/ml (10 ml) ampoule contains cisatracurium 2 mg/ml, as the besylate.
Each NIMBEX 5 vial contains cisatracurium 5 mg/ml, as the besylate.

PHARMACOLOGICAL CLASSIFICATION:
A 17.1 Peripherally-acting muscle relaxants.

PHARMACOLOGICAL ACTION:
Cisatracurium is an intermediate-duration, non-depolarising benzylisoquinolinium skeletal muscle relaxant. Cisatracurium binds to cholinergic receptors on the motor-end-plate to antagonise the action of acetylcholine, resulting in a competitive block of neuromuscular transmission. This action is readily reversed by anticholinesterase agents such as neostigmine or edrophonium.
Pharmacokinetic properties:
Cisatracurium undergoes degradation in the body at physiological pH and temperature by Hofmann elimination to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Elimination of cisatracurium is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites. These metabolites do not possess neuromuscular blocking activity.
Pharmacokinetics in Adult Patients: The ED_{95} (dose required to produce 95 % depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of cisatracurium is estimated to be 0,05 mg/kg bodyweight during opioid anaesthesia (thiopentone/fentanyl/midazolam). The ED_{95} of cisatracurium besylate in children during halothane anaesthesia is 0,04 mg/kg.
Non-compartmental pharmacokinetics of cisatracurium are independent of dose in the range studied (0,1 to 0,2 mg/kg, i.e. 2 to $4xED_{95}$). Pharmacokinetic parameters after doses of 0,1 and 0,2 mg/kg NIMBEX Injection administered to healthy adult surgical patients are summarised in the table below.

Parameter	Range of mean values
Clearance	4,7 to 5,7 ml/min/kg
Volume of distribution at steady state	121 to 161 ml/kg
Elimination half-life	22 to 29 min

Pharmacokinetics in Elderly Patients: There are no clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients.
Pharmacokinetics in Patients with Renal Impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure and in healthy adult patients. The recovery profile of cisatracurium is unchanged in the presence of renal failure.
Pharmacokinetics in Patients with Hepatic Impairment: There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage liver disease and in healthy adult patients. The recovery profile was unchanged.
Pharmacokinetics During Infusions: The pharmacokinetics of cisatracurium after infusions of NIMBEX Injection are similar to those after single bolus injection. The recovery profile after infusion of NIMBEX Injection is independent of duration of infusion and is similar to that after single bolus injections.
Pharmacokinetics in Intensive Care Unit (ICU) Patients: The pharmacokinetics of cisatracurium in ICU patients receiving prolonged infusions are similar to those in healthy surgical adults receiving infusions or single bolus injections. The recovery profile after infusions of NIMBEX Injection in ICU patients is independent of duration of infusion. When laudanosine was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation. However, there is no evidence that laudanosine has caused such effects in man even after prolonged infusions of cisatracurium to ICU patients with impaired renal and/or hepatic function.

INDICATIONS:
NIMBEX is used during surgical procedures to relax skeletal muscles and to facilitate controlled ventilation. NIMBEX is suitable for endotracheal intubation especially where subsequent muscle relaxation is required.

CONTRA-INDICATIONS:
NIMBEX Injection is contra-indicated in patients known to be hypersensitive to cisatracurium, atracurium, or benzenesulphonic acid.
Use and safety in pregnancy and lactation has not been established.
Neonates, as NIMBEX Injection has not been studied in this patient population.

WARNINGS:
CISATRACURIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES BUT HAS NO EFFECT ON CONSCIOUSNESS OR PAIN THRESHOLD. NIMBEX INJECTION SHOULD ONLY BE ADMINISTERED BY OR UNDER THE SUPERVISION OF AN ANAESTHETIST. FACILITIES FOR TRACHEAL INTUBATION AND MAINTENANCE OF PULMONARY VENTILATION AND ADEQUATE ARTERIAL OXYGENATION MUST BE AVAILABLE. MONITORING OF NEUROMUSCULAR FUNCTION IS RECOMMENDED DURING THE USE OF NIMBEX INJECTION IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.
NIMBEX is hypotonic and must not be administered into the infusion line of a blood transfusion.
ICU Patients: When laudanosine, a metabolite of cisatracurium, was administered to experimental animals, high concentrations were associated with hypotension and, in some species, cerebral excitation.

DOSAGE AND DIRECTIONS FOR USE:
Use by intravenous bolus injection:
Dosage in adults:
Tracheal Intubation: The recommended intubation dose of NIMBEX Injection for adults is 0,15 mg/kg. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection. Higher doses will shorten the time to onset of neuromuscular block. The following table summarises mean pharmacodynamic data when NIMBEX Injection was administered at doses of 0,1 to 0,4 mg/kg to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anaesthesia.

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90 % T_1* Suppression (min)	Time to Maximum T_1* Suppression (min)	Time to 25 % Spontaneous T_1* Recovery (min)
0,1	Opioid	3,4	4,8	45
0,15	Propofol	2,8	3,5	55
0,2	Opioid	2,4	2,9	65
0,4	Opioid	1,5	1,9	91

* Single twitch response as well as the first component of the Train-of-Four response of the adductor pollicis muscle following supramaximal electrical stimulation of the ulnar nerve.

Maintenance: Neuromuscular block can be extended with maintenance doses of NIMBEX Injection. A dose of 0,03 mg/kg provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anaesthesia. Consecutive maintenance doses do

Infusion Delivery Rate of NIMBEX Injection 2 mg/ml

Patient Weight (kg)	Dose (µg/kg/min)				Infusion Rate
	1,0	1,5	2,0	3,0	
20	0,6	0,9	1,2	1,8	ml/hr
70	2,1	3,2	4,2	6,3	ml/hr
100	3,0	4,5	6,0	9,0	ml/hr

Steady rate continuous infusion of NIMBEX Injection is not associated with a progressive increase or decrease in neuromuscular blocking effect.
Following discontinuation of infusion of NIMBEX Injection, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.
Dosage in neonates aged less than 1 month:
No dosage recommendation for neonates can be made until further information becomes available.
Dosage in elderly patients:
No dosing alterations are required in elderly patients. In these patients NIMBEX Injection has a similar pharmacodynamic profile to that observed in young adult patients, but as with other neuromuscular blocking agents, it may have a slightly slower onset.
Dosage in patients with renal impairment:
No dosing alterations are required in patients with renal failure. In these patients, NIMBEX Injection has a similar pharmacodynamic profile to that observed in patients with normal renal function, but it may have a slightly slower onset.
Dosage in patients with hepatic impairment:
No dosing alterations are required in patients with end-stage liver disease. In these patients NIMBEX Injection has a similar pharmacodynamic profile to that observed in patients with normal hepatic function but it may have a slightly faster onset.
Dosage in patients with cardiovascular disease:
NIMBEX has been used to provide neuromuscular block in patients undergoing cardiac surgery. When administered by rapid bolus injection (over 5 to 10 seconds) to patients with serious cardiovascular disease, NIMBEX has not been associated with clinically significant cardiovascular effects in any dose studied (up to and including 0,4 mg/kg (8x ED_{95})).
Dosage in Intensive Care Unit (ICU) patients:
NIMBEX Injection may be administered by bolus dose and/or infusion to adult patients in the ICU. An initial infusion rate of NIMBEX Injection of 3 µg/kg/min (0,18 mg/kg/hr) is recommended for adult ICU patients. There may be wide interpatient variation in dosage requirements and these may increase or decrease with time. In clinical studies the average infusion rate was 3 µg/kg/min (range 0,5 to 10,2 µg/kg/min [0,03 to 0,6 mg/kg/hr]). The median time to full spontaneous recovery following long-term (up to 6 days) infusion of NIMBEX Injection in ICU patients was approximately 50 minutes.

Infusion Delivery Rate of NIMBEX Injection 5 mg/ml

Patient Weight (kg)	Dose (µg/kg/min)				Infusion Rate
	1,0	1,5	2,0	3,0	
70	0,8	1,2	1,7	2,5	ml/hr
100	1,2	1,8	2,4	3,6	ml/hr

The recovery profile after infusions of NIMBEX Injection to ICU patients is independent of duration of infusion.
Dosage in patients undergoing hypothermic cardiac surgery:
There have been no studies of NIMBEX Injection in patients undergoing surgery with induced hypothermia (25 to 28 °C). The rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.
Dilution:
Diluted NIMBEX Injection is physically and chemically stable for at least 12 hours at 5 °C and 25 °C at concentrations between 0,1 and 2,0 mg/ml in the following infusion fluids, in either polyvinyl chloride (PVC) or polypropylene containers:
Sodium Chloride (0,9 % m/v) Intravenous Infusion, Glucose (5 % m/v) Intravenous Infusion, Sodium Chloride (0,18 % m/v) and Glucose (4 % m/v) Intravenous Infusion, Sodium Chloride (0,45 % m/v) and Glucose (2,5 % m/v) Intravenous Infusion.
However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use. Administration should commence as soon as possible thereafter and any remaining solution should be discarded.
NIMBEX Injection is not chemically stable when diluted with Lactated Ringer's Injection.
NIMBEX Injection has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port: alfentanil hydrochloride, droperidol, fentanyl citrate, midazolam hydrochloride and sufentanil citrate. Where other drugs are administered through the same indwelling needle or cannula as NIMBEX Injection, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g. Sodium Chloride Intravenous Infusion 0,9 % (m/v).
Since NIMBEX Injection is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions, e.g. sodium thiopentone. It is not compatible with ketorolac, trometamol or propofol injectable emulsion.
When a small vein is selected as the injection site, NIMBEX Injection should be flushed through the vein with a suitable intravenous fluid, e.g. Sodium Chloride Intravenous Infusion (0,9 % m/v).

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
No adverse experiences occurred during the clinical development programme that were considered to be reasonably attributable to NIMBEX Injection. Adverse experiences, considered possibly attributable, occurred with a frequency of less than 0,5 %. These were cutaneous flushing or rash, bradycardia, hypotension and bronchospasm.
Severe anaphylactic reactions have been reported in patients receiving NIMBEX in conjunction with one or more anaesthetics.
There have been some reports of persistent muscle weakness and/or myopathy following prolonged use of NIMBEX in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids.
Precautions:
Great caution should be exercised when administering NIMBEX Injection to patients who have shown allergic hypersensitivity to other neuromuscular blocking agents since cross reactivity between neuromuscular blocking agents has been reported.
Cisatracurium does not have significant vagolytic or ganglion-blocking properties. Consequently, NIMBEX Injection has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.
Patients with myasthenia gravis and other forms of neuromuscular disease have shown greatly increased sensitivity to non-depolarising blocking agents. An initial dose of not more than 0,02 mg/kg NIMBEX Injection is recommended in these patients.
Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents.
NIMBEX Injection has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that cisatracurium does not trigger this syndrome.
Cisatracurium has not been studied in patients with burns; however, as with other non-depolarising neuromuscular blocking agents, the possibility of increased dosing requirements and shortened duration of action must be considered if NIMBEX Injection is administered to these patients.
Interactions:
Many drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents, including the following:
Increased effect:
Anaesthetics: Volatile agents such as enflurane, isoflurane and halothane.
Ketamine.
Other non-depolarising neuromuscular blocking agents.
Other drugs:

- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- anti-arrhythmic drugs, including propranolol, calcium channel blockers, lignocaine, procainamide and quinidine
- diuretics, including furosemide and possibly thiazides, mannitol and acetazolamide
- magnesium salts
- lithium salts

not result in progressive prolongation of effect.
Spontaneous Recovery: Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the NIMBEX dose. During opioid or propofol anaesthesia, the median times from 25 to 75 % and from 5 to 95 % recovery are approximately 13 and 30 minutes, respectively.
Reversal: Neuromuscular block following NIMBEX administration is reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75 % recovery and to full clinical recovery (T_4/T_1 ratio ≥0,7) are approximately 4 and 9 minutes respectively, following administration of the reversal agent at an average of 10 % T_1 recovery.

Dosage in paediatric patients aged 1 month to 12 years:
Tracheal Intubation: As in adults, the recommended intubation dose of NIMBEX Injection is 0,15 mg/kg administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of NIMBEX. Pharmacodynamic data for this dose are presented in the tables below. If a shorter clinical duration is required, pharmacodynamic data suggest that a dose of 0,1 mg/kg may produce similar intubation conditions at 120 to 150 seconds.
In paediatric patients aged 1 month to 12 years, NIMBEX has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anaesthetic conditions. Small differences in the pharmacodynamic profile were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarised in the tables below.

Paediatric Patients aged 1 to 11 months:

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90 % Suppression (min)	Time to Maximum Suppression (min)	Time to 25 % Spontaneous T_1 Recovery (min)
0,15	Halothane	1,4	2,0	50
0,15	Opioid	1,4	2,0	47

Paediatric Patients aged 1 to 12 years:

Initial NIMBEX Injection Dose (mg/kg)	Anaesthetic Background	Time to 90 % Suppression (min)	Time to Maximum Suppression (min)	Time to 25 % Spontaneous T_1 Recovery (min)
0,08	Halothane	1,7	2,5	31
0,1	Opioid	1,7	2,8	28
0,15	Halothane	2,3	3,0	43
0,15	Opioid	2,6	3,6	38

Halothane may be expected to extend the clinically effective duration of a dose of NIMBEX by up to 20 %. No information is available on the use of NIMBEX in children during isoflurane anaesthesia but these agents may also be expected to extend the clinically effective duration of a dose of NIMBEX by up to 20 %.
Maintenance: Neuromuscular block can be extended with maintenance doses of NIMBEX Injection. A dose of 0,02 mg/kg provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anaesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.
Spontaneous Recovery: Once recovery from neuromuscular block is underway, the rate is independent of the NIMBEX dose administered. During opioid or halothane anaesthesia, the median times from 25 to 75 % and from 5 to 95 % recovery are approximately 11 and 28 minutes, respectively.
Reversal: Neuromuscular block following NIMBEX administration is reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75 % recovery and to full clinical recovery (T_4/T_1 ratio ≥0,7) are approximately 2 and 5 minutes respectively, following administration of the reversal agent at an average of 13 % T_1 recovery.

Use by intravenous infusion:

Dosage in adults and children aged 2 to 12 years:
Maintenance of neuromuscular block may be achieved by infusion of NIMBEX Injection. An initial infusion rate of 3 µg/kg/min (0,18 mg/kg/hr) is recommended to restore 89 to 99 % T_1 suppression following evidence of spontaneous recovery. After an initial period of stabilisation of neuromuscular block, a rate of 1 to 2 µg/kg/min (0,06 to 0,12 mg/kg/hr) should be adequate to maintain block in this range in most patients.
Reduction of the infusion rate by up to 40 % may be required when NIMBEX Injection is administered during isoflurane or enflurane anaesthesia (see INTERACTIONS). The infusion rate will depend upon the concentration of cisatracurium in the infusion solution, the desired degree of neuromuscular block, and the patient's weight. The following table provides guidelines for delivery of undiluted NIMBEX Injection.

- ganglion blocking drugs: trimetaphan, hexamethonium.

Decreased effect:
Prior chronic administration of phenytoin or carbamazepine.
Prior administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of NIMBEX Injection or on infusion rate requirements.
Administration of suxamethonium to prolong the effects of non-depolarising neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases.
Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarising neuromuscular blocking agents might result. Such drugs include various antibiotics, beta-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with NIMBEX Injection.
It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired by NIMBEX Injection. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

IDENTIFICATION:
A clear, pale yellow or greenish yellow solution, free from visible particulate matter.

PRESENTATION:
NIMBEX 2 mg/ml (2,5 ml) Injection: Box of 5 ampoules
NIMBEX 2 mg/ml (5 ml) Injection: Box of 5 ampoules
NIMBEX 2 mg/ml (10 ml) Injection: Box of 5 ampoules
NIMBEX 5: Box with one 30 ml vial

STORAGE INSTRUCTIONS:
Unopened ampoule/vial:
Keep out of reach of children.
Store between 2 °C and 8 °C.
Do not freeze.
Protect from light.
In addition, the diluted solution can be stored at 5 °C or 25 °C.
This product is marketed as a single dose ampoule/vial and any unused portion of the solution must be discarded.
The ampoule/vial must not be removed from the outer carton until such time as it is required for administration.

REGISTRATION NUMBER:
NIMBEX 2 mg/ml (2,5 ml) Injection : 31/17.1/0255
NIMBEX 2 mg/ml (5 ml) Injection: 31/17.1/0444
NIMBEX 2 mg/ml (10 ml) Injection: 31/17.1/0445
NIMBEX 5 Injection: 31/17.1/0256

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:
GlaxoSmithKline South Africa (Pty) Ltd
39 Hawkins Avenue
Epping Industria 1, 7460

DATE OF PUBLICATION OF THE PACKAGE INSERT:
27 November 1998

QDS-7

Nimbex:
Nimbex 2 mg/ml (2,5 ml): Reg No 04/17.1/0929 [NS2]
Nimbex 2 mg/ml (5 ml): Reg No 04/17.1/0928 [NS2]
Nimbex 2 mg/ml (10 ml): Reg No 04/17.1/0927 [NS2]
Nimbex 5: Reg No 04/17.1/0935 [NS2]

GlaxoSmithKline

Scheduling status S4

Proprietary name (and dosage form)

SPEC OXYTOCIN 10 I.U. Ampoule, SPEC OXYTOCIN 5 I.U. Ampoule

Composition
SPEC OXYTOCIN 10 is available in 1ml ampoules containing (16,66 µg/ml) synthetic oxytocin. Each 1ml ampoule contains 10 I.U. synthetic oxytocin.
SPEC OXYTOCIN 5 is available in 1ml ampoules containing (8,33 µg/ml) synthetic oxytocin. Each 1ml ampoule contains 5 I.U. synthetic oxytocin.
Pharmacological Classification A.19: Oxytocics.
Pharmacological action The active principle of oxytocin injection is a synthetic nonapeptide identical to oxytocin, a hormone released by the posterior lobe of the pituitary. Oxytocin exerts a stimulatory effect on the smooth musculature of the uterus, particularly towards the end of pregnancy, during labour, after delivery and in the puerperium, i.e. at times when the number of specific oxytocin receptors in the myometrium is increased. When given by low-dose intravenous infusion, oxytocin elicits rhythmic uterine contractions that are indistinguishable in frequency, force and duration from those observed during spontaneous labour.
At higher infusion dosages, or when given by single injection, the substance is capable of causing sustained tetanic contractions.

Being synthetic, oxytocin does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like anti-diuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid intravenous bolus injection, consists in a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia.
Pharmacokinetics When administered by intravenous or intramuscular injection for prevention or treatment of postpartum haemorrhage, oxytocin acts rapidly with a latency period of less than 1 minute by intravenous injection, and of 3 to 7 minutes by the intramuscular route. The oxytocic response lasts for 30 to 60 minutes after intramuscular administration; it may be shorter with intravenous injection.
When oxytocin is given by continuous intravenous infusion at doses appropriate for induction or enhancement of labour, the uterine response sets in gradually and reaches a steady state usually within 20 to 60 minutes. The corresponding plasma levels of oxytocin are comparable to those measured during spontaneous first-stage labour. Upon discontinuation of the infusion, or following a substantial reduction in the infusion rate, i.e. in the case of overstimulation, uterine activity declines rapidly, but may continue on an adequate lower level. The relative ease with which the rate and force of uterine contractions can be regulated by the intravenous infusion of oxytocin is due to the short half-life of oxytocin. Plasma protein-binding is very low. Removal of oxytocin from plasma is accomplished mainly by the liver and the kidneys. Less than 1 % of a given dose is excreted unchanged in the urine. The apparent volume of distribution is approximately 300 ml/kg in men and the metabolic clearance rate amounts to about 20 ml/kg per minute in men as well as in pregnant women. The extent to which oxytocin crosses the placenta or passes into breast milk is not known.
Indications
- Induction of labour for medical reasons, e.g. in cases of post-term gestation, premature rupture of the membranes, pregnancy induced hypertension (pre-eclampsia).
- Enhancement of labour in selected cases of uterine inertia.
- During Caesarean section, following the delivery of the child.
- Prevention and treatment of postpartum haemorrhage and uterine atony.

Contra-indications
Hypersensitivity to the agent.
Hypertonic uterine contractions. Foetal distress. When delivery is not imminent. Any conditions in which for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated, e.g. significant cephalopelvic disproportion, foetal malpresentation, placenta praevia and vasa praevia, placental abruption, cord presentation or prolapse, overdistention or impaired resistance of the uterus to rupture as in multiple pregnancy, polyhydramnios, grand multiparity and in the presence of a uterine scar resulting from major surgery, including classical Caesarean section.
SPEC OXYTOCIN should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.
WARNINGS SPEC OXYTOCIN should not be given the same time as other oxytocics. (Also see "Precautions").
INTERACTIONS Prostaglandins may potentiate the uterotonic effect of SPEC OXYTOCIN and vice versa, therefore concomitant administration requires very careful monitoring.
Some inhalation anaesthetics, e.g. cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with SPEC OXYTOCIN has also been reported to cause cardiac rhythm disturbances.
When given during or after caudal block anaesthesia, SPEC OXYTOCIN may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.
Pregnancy and Lactation Oxytocin causes uterine birth contractions and milk ejection during lactation.
Dosage and directions for use
- **Induction or enhancement of labour.**

SPEC OXYTOCIN should be administered as an intravenous drip infusion or preferably by means of a variable-speed infusion pump.
For drip infusion, it is recommended that 5 I.U. of SPEC OXYTOCIN be added to 500 ml of a physiologic electrolyte solution. For patients in whom infusion of sodium chloride must be avoided, 5 % dextrose solution may be used as the diluent (see "Precautions"). To ensure even mixing the bottle or bag must be turned upside-down several times before use. The initial infusion rate should be set at 1 to 4 milliunits (0,1 to 0,4 ml/min or 2 to 8 drops/min).
It may be gradually increased at intervals not shorter than 20 minutes until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10 milliunits/min (1 ml/min or 20 drops/min) and the recommended maximum rate is 20 milliunits/min (2 ml/minute = 40 drops per minute). In the unusual event that higher rates are required, as may occur in the management of foetal death in utero or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to SPEC OXYTOCIN, it is advisable to use a more concentrated SPEC OXYTOCIN solution e.g. 10 I.U. in 500 ml.
When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump. The frequency, strength and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine contractions is attained, the infusion rate can be reduced.
The SPEC OXYTOCIN infusion should be discontinued immediately in the event of uterine hyperactivity or foetal distress. If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 I.U. SPEC OXYTOCIN, it is recommended that the attempt to induce labour should be ceased; it may be repeated on the following day starting again from a rate of 1 to 4 milliunits/min (0,1 to 0,4 ml/min or 2 to 8 drops/minute).
Inadvertent paravenous infusion of SPEC OXYTOCIN is not harmful.
Caesarean section: 5 I.U. intramurally immediately after delivery of the foetus.
- **Prevention of postpartum uterine haemorrhage** The usual dose is 5 I.U. slowly intravenously or 5 to 10 I.U. intramuscular after delivery of the placenta. In women given SPEC OXYTOCIN for induction of labour, the infusion rate should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.
- **Treatment of postpartum uterine haemorrhage** The usual dose is 5 to 10 I.U. i.m. followed in severe cases by intravenous infusion of a solution containing 5 to 20 I.U. of SPEC OXYTOCIN in 500 ml of a non-hydrating diluent, run at the rate necessary to control uterine atony.
- **Incomplete, inevitable or missed abortion** 5 I.U. slowly intravenous. If necessary followed by intravenous infusion at a rate of 20 to 40 milliunits/min or higher.

Side effects and special precautions
Side Effects
When SPEC OXYTOCIN is used by i.v. infusion for the induction or enhancement of labour, its administration at too high doses results in uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions or rupture of the uterus.
With either mode of administration (intramuscular or intravenous) SPEC OXYTOCIN may cause nausea, vomiting or cardiac arrhythmias. The table below contains adverse effects with possible, probable or unknown relationship to the use of oxytocin.

Organ System	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10 000, <1/1000)
Cardiovascular		Short-lasting hypotension accompanied by flushing and reflex tachycardia	Cardiac arrythmias	Anaphylactoid reaction resulting in shock
Gastro-intestinal disorders		Nausea,vomiting		
Blood and lymphatic disorder				Post-partum hemorrhage and fatal afibrinogenaemia due to obstetric complications
Respiratory		Dyspnoea		
Skin and appendages		Rash		

Others:
Prolonged or too rapid infusion of SPEC OXYTOCIN has an anti-diuretic effect, which may cause transient water intoxication. Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of SPEC OXYTOCIN together with large amounts of electrolyte-free fluid were administered over a prolonged period of time (See "Precautions").
Pelvic haematomas, neonatal jaundice and retinal haemorrhage have been associated with the use of SPEC OXYTOCIN.
Rarely, maternal death from severe hypertension and subarachnoid haemorrhage has occurred.
Precautions
The induction of labour by means of SPEC OXYTOCIN should be attempted only when strictly indicated for medical reasons rather than for convenience. Administration should only be under hospital conditions and qualified medical supervision.
When given for induction and enhancement of labour, SPEC OXYTOCIN must only be administered as an intravenous infusion, and never by subcutaneous, intramuscular or intravenous bolus injection. Careful monitoring of foetal heart rate and uterine motility (frequency, strength and duration of contractions) is essential so that dosage may be adjusted to individual response. When SPEC OXYTOCIN is given for induction of labour, particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease and in patients above 35 years of age or with a history of lower-uterine-segment Caesarean section. Infusion volume should be low in patients with cardiovascular disorders. In the case of foetal death in utero and/or in the presence of meconium-stained amniotic fluid, tumultuous labour must be avoided, as it may cause amniotic fluid embolism. Because SPEC OXYTOCIN possesses slight anti-diuretic activity, its prolonged intravenous administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage may cause water intoxication associated with hyponatraemia.
To avoid this rare complication, the following precautions must be observed whenever high doses of SPEC OXYTOCIN are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low by infusing SPEC OXYTOCIN at a higher concentration than recommended for the induction or enhancement of labour at term; fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.
When SPEC OXYTOCIN is used for prevention or treatment of uterine haemorrhage, rapid intravenous injection should be avoided, as it may cause an acute short-lasting drop in blood pressure.
Known symptoms of overdosage and particulars of its treatment
See "Side effects and Special Precautions". In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported. Overdosage following prolonged or too rapid infusion, may give rise to the following complications: foetal distress (bradycardia and arrhythmias, meconium staining of amniotic fluid, foetal asphyxia). Uterine hypertonicity, tetanic contraction, uterine rupture, extensive laceration of soft tissue, subarachnoid haemorrhage, severe hypotension, water retention and intoxication with convulsions, coma and even foetal and maternal death.
Treatment
When signs/symptoms of overdosage occur during continuous i.v. administration of SPEC OXYTOCIN, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance and control convulsions that may eventually occur by judicious use of diazepam.
Identification
SPEC OXYTOCIN 10 I.U. A clear, colourless solution, free from visible particles. **SPEC OXYTOCIN 5 I.U.** A clear, colourless solution, free from visible particles.
Presentation
SPEC OXYTOCIN 10 I.U. 1ml clear glass ampoule coded with single magenta-coloured ring on the neck of the ampoule.
Carton of 5 or 10 ampoules of 1 ml each.
SPEC OXYTOCIN 5 I.U. 1ml clear glass ampoules coded with two magenta-coloured rings on the neck of the ampoule. Carton of 5 or 10 ampoules of 1 ml each.
Storage instructions
Store in a refrigerator between 2 and 8 °C. Do not freeze. Do not remove the ampoule from the carton until required for use.
Protect from direct light. Discard any unused potion.
SPEC OXYTOCIN AMPOULES SHOULD BE KEPT OUT OF REACH OF CHILDREN.
Registration numbers:
SPEC OXYTOCIN 10 I.U.: A39/19/0074 Namibia: SPEC OXYTOCIN 10 I.U., Reg. No. 08/19/0106 Botswana: SPEC OXYTOCIN 10 I.U., Reg. No. BOT0701011 Zimbabwe: PP.SPEC OXYTOCIN 10,Reg.No. 2013/21.1.1/4804
SPEC OXYTOCIN 5 I.U.: 41/19/0303 Namibia: SPEC OXYTOCIN 5 I.U., Reg. No. 08/19/0107
Name and business address of the applicant
Specpharm (Pty) Ltd, cnr 15th Road and Pharmaceutical Road, Halfway House, Midrand, Gauteng
Date of publication of this package insert 10 August 2007

novo nordisk

Actrapid® HM (ge)

100 units/ml

Scheduling status:
S3

Proprietary name and dosage form:
Actrapid® HM (ge) Injection

Composition:
Each ml of bio-synthetic human soluble insulin contains 100 units of a sterile solution of genetically engineered monocomponent neutral insulin, preserved with 0.3% m-cresol.

Pharmacological classification:
A 21.1 Insulin preparations

Pharmacological action:
Pharmacodynamic properties
Actrapid® HM (ge) insulin is a fast acting soluble insulin.
Replaces the insufficiency of insulin secretion by the beta-cells of the pancreas.
The blood glucose lowering effect of insulin occurs when the molecules facilitate the uptake of glucose by binding to insulin receptors on muscle and fat cells and simultaneously inhibit the output of glucose from the liver.
The effect of soluble insulin after subcutaneous administration begins after approximately ½ hour, reaches maximal effect between 1.5 and 3.5 hours and the entire duration of action is approximately 7 - 8 hours.

Pharmacokinetic properties
Insulin in the blood stream has a half life of a few minutes. Consequently the time action profile of an insulin preparation is determined solely by its absorption characteristics.
This process is influenced by several factors (e.g. insulin dosage, injection route and site).
The pharmacokinetics of insulins are therefore affected by significant intra- and inter-individual variation.

Absorption
The maximum plasma concentration of soluble insulin is reached within 1.5 - 2.5 hours after subcutaneous administration.

Distribution
No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Indications:
Diabetes Mellitus

Contra-indications:
Hypoglycaemia
Hypersensitivity to human insulin or any of the excipients.

Warnings:
Inadequate dosing or discontinuation of treatment may, especially in Type 1 diabetes (insulin dependent diabetes mellitus), lead to hyperglycaemia.
The first symptoms of hyperglycaemia usually come on gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath.
In Type 1 diabetes, untreated hyperglycaemic events are potentially lethal.
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia.
Patients, whose blood glucose control is greatly improved by e.g. intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.
Transferring a patient to a new type or brand of insulin should be done under strict medical supervision.
Changes in strength, brand, type, species (animal, human, human insulin analogue) and/or method of manufacture may result in a change in dosage from that used with their usual insulin. If an adjustment is needed, it may be done with the first dose or during the first few weeks or months.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.
Before travelling between different time zones, the patient should be advised to consult the doctor, since this may mean that the patient has to take insulin and meals at different times.
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.
Actrapid® HM (ge) is not recommended for use in infusion pumps for continuous subcutaneous insulin infusion due to the risk of precipitation in some pump catheters.

Interactions:
A number of medicines are known to interact with glucose metabolism.

The following substances may reduce the patient's insulin requirements:
Oral hypoglycaemic agents (OHAs), monoamine oxidase inhibitors (MAOI), non-selective beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates and alcohol.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.
Beta blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.
Octreotide/lanreotide may both decrease and increase insulin requirements.
Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Pregnancy and lactation:
There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.
If untreated during pregnancy, diabetes mellitus constitutes a risk in intrauterine development.
Diabetes therapy must therefore be continued during pregnancy.
Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and deaths in utero.
Intensified blood glucose control and monitoring of pregnant women with diabetes is recommended throughout pregnancy and when contemplating a pregnancy.
Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy values.
There are no restrictions on the treatment of diabetes with Actrapid® HM (ge) during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However the dosage, diet or both may need to be adjusted.

Dosage and directions for use:
The dosage for each patient is individual and determined by his doctor in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg/day. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual endogenous insulin production.
In patients with diabetes mellitus, optimized metabolic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.
Actrapid® HM (ge) is administered subcutaneously in the thigh or abdominal wall. If convenient the gluteal or deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.
Injection sites should be rotated within an anatomical region in order to avoid lipodystrophy. Injection into a lifted skin fold minimizes the risk of intramuscular injection. Keep the needle under the skin for at least 6 seconds to make sure the entire dose is injected.
Actrapid® HM (ge) may also be administered intravenously, which should only be carried out by health-care professionals.
Renal or hepatic impairment may reduce insulin requirement.

Injections using 10 ml vials and conventional syringes.
Clean the skin. Wipe the rubber disc on the vial with alcohol. Draw the piston of the syringe out to a distance corresponding to the quantity of insulin required. Gently agitate the vial of insulin. Then pierce the rubber disc with the needle, push the piston home, and turn the vial upside down. Draw the required amount of insulin into the syringe. Avoid air in the syringe and needle by working the piston slightly up and down. Make the injection at a suitable depth under the skin (subcutaneously). It is important that the injection is made with a syringe which is marked for use with an insulin preparation containing 100 units per ml. Failure to use the correct syringe, can lead to dosage errors.

Side effects and special precautions:
Side effects observed in patients using Actrapid® HM (ge) are mainly dose-dependent and due to the pharmacological effect of insulin. As for other insulin products, hypoglycaemia in general is the most frequent side effect. It may occur if the insulin dose is too high in relation to the insulin requirement.
In clinical trials and during marketed use, the frequency varies with the patient population and dose regimens therefore no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.
Frequencies of side effects from clinical trials, which by an overall judgment are considered related to Actrapid® HM (ge) are listed below. The frequencies are defined as: Uncommon (≥1/1,000, <1/100).
Isolated spontaneous cases are presented as very rare, defined as: <1/10,000.

Immune system disorder
Uncommon - Urticaria, rash
Very rare - Anaphylactic reactions
Symptoms of generalized hypersensitivity may include general skin rash, itching, sweating, gastrointestinal upset, and angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. General and hypersensitivity reactions are potentially life threatening.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed "acute painful neuropathy" which is usually reversible.

Eye disorders
Very rare - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Uncommon - Diabetic retinopathy
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous disorders
Uncommon - Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within the same area.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.

Special Precautions
Effects on ability to drive and use machines:
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).
Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Known symptoms of overdosage and particulars of its treatment:
A specific overdose of insulin cannot be defined, however hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirements are administered.

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or glucose given intravenously by a medical professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

Identification:
A colourless liquid free from turbidity and foreign matter.

Presentation:
Actrapid® HM (ge) vial, 10 ml vial made of glass (type 1). The vial is closed with a rubber closure and packed in a carton.
Snap-off caps:
The insulin vials are packed and shipped with a protective, colour coded, tamper-proof plastic cap. In order to withdraw insulin from a new vial, the cap must be removed. If the cap is not securely fastened to a newly purchased vial, return the vial to the pharmacy.

Storage instructions:
Do not freeze.
Keep out of sunlight.
Keep out of reach of children.
Insulin vials not in use to be stored between 2 °C and 8 °C (in a refrigerator).
Actrapid® HM (ge) vial in use may be kept at room temperature (max. 25 °C) for one month.
Note: Actrapid® HM (ge) should not be used if not water-clear and colourless.
Never use insulin after expiry date.

Appendix D: Digital thermometer

TL8001B

Quick Details

Place of Origin: Guangdong, China (Mainland)	Brand Name: TLX	Model Number: TL8001B
	Usage: Household	Theory: Temperature Sensor
Measuring temperature range: -20 °c~70 °c (-58°F~158°F)	Measuring humidity range: 10%~99%TH	Accuracy: ±1°c(or ±2°F), ±5%RH
	Resolution: 0.1 °c(0.1°F)&1%RH	Display comfort level: comfort, wet or dry
Selectable temperature unit: C/F	Key feature: Max/Min memory	Dimensions: 110*100*20mm
Power supply: 1.5V	Net weight: 137g	

Appendix D: Digital Thermometer

Lasec

Lasec SA Pty Ltd

LASEC SA (PTY) LTD
HEAD OFFICE: CAPE TOWN
82 Old Mill Road, Ndabeni,
Cape Town, 7405, South Africa
PO Box 2110, Cape Town, 8000
+27 21 531 7504 +27 21 531 7582

JOHANNESBURG 011 082 2500 011 082 2699
DURBAN 031 702 6001 031 702 3008
PORT ELIZABETH 041 373 9173 041 374 8805
BLOEMFONTEIN 051 447 9500 051 447 1940
sales@lasec.co.za www.lasec.co.za
Registration No. 2000/010102/07 - VAT No. 4320190434

General Cash Account
Nadia Cloete,35 Elizabeth Eybers Street
Langenhovenpark,Bloemfontein

9301

Doc. Type	Pre Invoice
Date	8 January 2018
Page	1 of 3
Doc. Number	1712-500028013

Account Number	Customer Order Number	Customer VAT Number
51999		N/A

Stock Code	Description	Qty	Unit Of Measure	Unit Price Excl V.A.T.	Total Price Excl V.A.T.
H3THE006Z-000002	THERMOMETER DIGITAL DUAL IN/OUT W/ PROBE -50/70C	12	EA	127.00	1,524.00
	686 Units currently available. Subject to prior sale.				

SUB Total	R 1,524.00
VAT 14 %	R 213.36
Total incl. VAT	- R 1,737.36

Att: Nadia Cloete

Tel: 051 405 3307

BANKING DETAILS
ACCOUNT HOLDER: Lasec SA (Pty) Ltd
BANK: First National Bank
BRANCH: Claremont
B/CODE: 200109
ACC. NO.: 62283934406

Please see attached for the Special Terms and Conditions, and a link to LasecSA`s Standard Terms and Conditions.

Directors D.A. Darling N. Subramoney

Registration No. 2000/010102/07 | VAT No. 4320190434 | Lasec SA is a level 4 BBBEE Contributor
ISO9001:2008 certified company | ISO17025:2005 SANAS certified calibration laboratory

Appendix E: Data Capture Sheet

Data Capture Sheet						
Date:			Theatre number:			
Drug packaged ☐	Plastic container ☐		Original carton ☐		Loose	
Anaesthetic time	Start:		End:			
	07:30	09:00	11:00	13:00	15:00	17:00
Theatre Temp ^{0}C						
Cooler Box Temp ^{0}C						
Suxamethonium						
Rocuronium						
Atracurium						
Cis-Atracurium						
Phenylephrine						
Heparin 1000U						
Heparin 5000U						
Insulin						
Oxytocin						

Appendix F: Permission Letter Head of Department Anaesthesiology

Department of Anaesthesiology
University of the Free State
Bloemfontein
10 April 2018

Prof G Lamacraft
Acting Head of Department Anaesthesiology
University of Free State
Bloemfontein

Re: Permission for research study

I, Nadia Cloete, am a registrar in Anaesthesiology at University of Free State. To ensure the completion of my training I plan to conduct an observational descriptive study to determine whether the temperatures in our cold drug storage unit in the theatre suites at Universities Hospital Theatre comply with manufacture storage temperature recommendations.

I hereby request permission to test the temperature of the cooler boxes housing refrigerator drugs in the theatre suite 1-11 during the day time theatre list at the following time: 07:30, 09:00, and 11:00, 13:00; 15:00 and 17:00 for five consecutive days.

No patient data will be required for my research and the data analysis will be done by the Department of Statistics, University of Free State.

Regards

Nadia Cloete
Registrar Anaesthesiology
University of the Free State

Dr P Van Zyl
Consultant Department of Pharmacology
University of the Free State

Appendix G: Permission Letter – Matron of Universitas Theatre Complex

Department of Anaesthesiology
University of the Free State
Bloemfontein
10 April 2018

Matron P Seekoei
Matron Universities Hospital Theatre
Bloemfontein

Re: Permission for research study

I, Nadia Cloete, am a registrar in Anaesthesiology at University of Free State. To ensure the completion of my training I plan to conduct an observational descriptive study to determine whether the temperatures in our old drug storage units in the theatre suites at Universities Hospital Theatre comply with manufacture storage temperature recommendations.

I hereby request permission to test the ambient theatre temperature and the temperature of the cooler boxes housing refrigerator drugs in the theatre suite 1-11, on five consecutive days, during the day time theatre list at the following time: 07:30, 09:00, and 11:00, 13:00; 15:00 and 17:00.

For the five days of data collection nursing staff will be required to package the cooler boxes as per standard of practice for the theatres they are allocated too. I will request that at the end of the theatre list the cooler boxes remain in theatre till 17:00, thereafter I will personally collect and return it to the central storage medication refrigerator.

No patient data will be required for my research and the data analysis will be done by the Department of Statistics, University of Free State.

Regards

Nadia Cloete
Registrar Anaesthesiology
University of the Free State

Dr P Van Zyl
Consultant Department of Pharmacology
University of the Free State

Appendix H: Study Notice on the Cold Drug Storage Unit

ATTENTION

Please note that this cooler box is part of a study. **Do not** tamper with the contents unless to remove or replenish drugs as per anaesthetic requirement.

Please **DO NOT REMOVE** this cooler box at the end of the theatre list

Thank you

Appendix I

Synchronization reading procedure

Aim

To ensure that all 12 thermometers used in this study measure the same temperature (taking into account the manufacturers accuracy of 1^0C).

Procedure

The measuring probe of the thermometer will be placed in a constant temperature environment and allow to equilibrate for 5mins. This will be done at two temperatures:

Close to zero centigrade: The Styrofoam® cooler box will be filled with water and ice cubes floating it in. The thermometers measuring probe will be placed inside and after 5 mins of equilibration the reading will be noted and recorded for reference purposes.

Close to room temperature: The thermometers measuring probe will be placed in a closed Styrofoam® cooler box in a room with the air conditioner off and door closed (to limit the effect of air movement), allowed 5 minutes to equilibrate. This reading will be noted and recorded for reference purposes.

This will be performed on the on the day of the pilot study prior to data collection.

L: Data collection form

Please note that a row was inserted on the Data Capture Sheet to document the size, number and position of eutectic gel pack placement within the cooler box.

Data Capture Sheet							
Date:			Theatre number:				
Drug packaged ☐	Plastic container ☐		Original carton ☐		Loose		
Anaesthetic time	Start:		End:				
		07:30	09:00	11:00	13:00	15:00	17:00
Theatre Temp ^{0}C							
Cooler Box Temp ^{0}C							
Amount of Drug Ampoules	Suxamethonium						
	Rocuronium						
	Atracurium						
	Cis-Atracurium						
	Phenylephrine						
	Heparin 1000U						
	Heparin 5000U						
	Insulin						
	Oxytocin						

M: Instructions to the Authors

Instructions for Authors

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The online submission process will prompt authors to check off the following declarations:

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3. Permission to publish licensed material (tables, figures, graphs) has been obtained and the letter of approval and proof of payment for royalties have been submitted as supplementary files.
4. The submitting/corresponding author is duly authorised to herewith assign copyright to the *South African Society of Anaesthesiologists (SASA)*.
5. All co-authors have made significant contributions to the manuscript to qualify as co-authors.
6. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
7. A conflict of interest statement has been included where appropriate.
8. The submission adheres to the instructions to authors in terms of all technical aspects of the manuscript.

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Article sections and length

The following contributions are accepted (word counts include abstracts, tables and references):

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All articles must have a title page with the following information and in this particular order:

1. Title of the article.
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4. Five keywords.

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All articles must include an abstract. The structured abstract for an Original Research article should be between 450 and 600 words and should consist of four paragraphs labelled Background, Methods, Results, and Conclusions. It should briefly describe the problem or issue being addressed in the study, how the study was performed, the major results, and what the authors conclude from these results. The abstracts for other types of articles should be no longer than 250 words and need not follow the structured abstract format. No reference numbers are allowed in an abstract.

Keywords

All articles should include keywords. Up to five words or short phrases should be used. Use terms from the Medical Subject Headings (MeSH) of *Index Medicus* when available and appropriate. Key words are used to index the article and may be published with the abstract.

Acknowledgements

In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References

Cite references in numerical order in the text, in superscript format (Format> Font> Click superscript), after the full stop or comma. Please do not use brackets and do not use the foot note function of MS Word. In the References section, references must be typed double-spaced and numbered consecutively in the order in which they are cited, not alphabetically.

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List all authors when there are six or fewer; when there are seven or more, list the first three, then "et al." When citing URLs to web documents, place in the reference list, and use the following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

The following are sample references:

1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging

process: volume assessment by 3-dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
2. Polgreen PM, Diekema DJ, Vandeberg J, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

A comprehensive reference guide can be found at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2

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Tables should be self-explanatory, clearly organised, and supplemental to the text of the manuscript. Each table should be headed by a clear descriptive title and numbered in Roman numerals (I, II, etc) in order of its appearance as called out in the text. Tables must be inserted in the correct position in the text. Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations.
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4. All author details (Full names, qualifications and affiliation) must be provided.
5. The full contact details of corresponding author (Tel, fax, e-mail, postal address) must be on the manuscript.
6. There must be an abstract and keywords.
7. References must strictly be in Vancouver format. (Reference numbers must be strictly numerical and be typed in superscript, not be in brackets and must be placed AFTER the full stop or comma.)
8. It must be clear where every figure and table should be placed in the text. If possible, tables and figures must be placed in the text where appropriate. If too large or impractical, they may be featured at the end of the manuscript or uploaded as separate supplementary files.
9. All photographs must be at 300dpi and clearly marked according to the figure numbers in the text. (Figure 1, Table II, etc.)
10. All numbers below ten, without percentages or units, must be written in words.
11. Figure numbers: Arabic, table numbers: Roman
12. The submission must be reviewed by a language expert proficient in UK English.

Thank you for your submission.

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UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Dr PM van Zyl
Department of Pharmacology

14th January 2020

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Dr PM van Zyl (supervisor)