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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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.
Acknowledgements

I would like to acknowledge the following people for their contribution to this research; for the input and discussion of practical daily situations arising in anaesthesia requiring questioning and research, for refining thought processes and creating a support network for budding academics.

Dr PM. van Zyl – my supervisor

Prof G. Lamacraft – generated the original idea for this research

Prof BJS. Diedericks – my mentor

Dr E. Turton – the Head of Department of Anaesthesiology at University of the Free State

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.
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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°C – 23,8°C with a median of 14,8°C. This method of drug storage was not conducive to store all temperature sensitive anaesthetic drugs (requiring storage at 2°C – 8°C) 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°C 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°C – 8°C 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°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°C...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.

*Abstract Word Count: 508*
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 2⁰C to 8⁰C.

Room temperature

Comfortable temperature range indoors, considered to be 20⁰C to 25⁰C.

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAH</td>
<td>Universitas Academic Hospital</td>
</tr>
<tr>
<td>HSREC</td>
<td>Health Sciences Research Ethics Committee</td>
</tr>
<tr>
<td>DOH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
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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 2⁰C – 8⁰C, 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 16\textsuperscript{th} October 1846 when WTG Morton demonstrated the use of a single agent anaesthesia, ether, to induce a sleep like state.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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°C – 8°C) 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.\textsuperscript{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.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Muscle relaxant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>50 mg/ml (2ml ampoule)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>Fresenius Kabi, Bodene (Pty) Ltd</td>
</tr>
<tr>
<td>Manufacturer Recommended</td>
<td></td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>2\textdegreeC – 8 \textdegreeC</td>
</tr>
</tbody>
</table>
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°C – 8°C), room temperature (20°C – 25°C) 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.**

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°C it was 0.3% compared to 8,1% at 37°C. 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.

<p>| Pharmacological classification | Muscle relaxant |</p>
<table>
<thead>
<tr>
<th>Concentration</th>
<th>10 mg/ml (5ml ampoule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer / Distributor</td>
<td>Biotech Laboratories (PTY) LTD.</td>
</tr>
<tr>
<td>Manufacturer Recommended Storage Temperature</td>
<td>2°C – 8°C</td>
</tr>
<tr>
<td>Additional Manufacturer Instructions</td>
<td>Protect from light. Do not freeze. Keep vial in outer carton until use required. Use immediately after first opening.</td>
</tr>
</tbody>
</table>
| 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°C – 29°C; median 25.1°C). 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.

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Muscle relaxant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>10 mg/ml (2.5 ml ampoule)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Manufacturer Recommended</td>
<td></td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>$2^\circ$C – $8^\circ$C</td>
</tr>
<tr>
<td>Additional Manufacturer</td>
<td></td>
</tr>
<tr>
<td>Instructions</td>
<td>Protect from light, Do not freeze</td>
</tr>
<tr>
<td>Recommendation by other studies</td>
<td><strong>Atracurium stored at room temperature for two weeks does not cause clinical significant degradation.</strong>$^{13}$</td>
</tr>
</tbody>
</table>

The aim of this study by Frasca et al. was to compare muscle relaxation when atracurium stored at recommended refrigerated temperature ($2^\circ$C – $8^\circ$C) and operating room temperature ($15^\circ$C – $20^\circ$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.

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Muscle relaxant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>2 mg/ml (2.5ml ampoule)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>GlaxoSmithKline</td>
</tr>
</tbody>
</table>
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°C – 8°C), room temperature (20°C – 25°C) 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.

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Vasopressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>10 mg/ml (1 ml ampoule)</td>
</tr>
<tr>
<td></td>
<td>100 mg/ml (0,5 ml ampoule, 10% solution)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>Biomed, S.A. Abbott (10 mg/ml)</td>
</tr>
<tr>
<td></td>
<td>Soflens (PTY) Ltd (10% solution)</td>
</tr>
<tr>
<td>Manufacturer Recommended Storage Temperature</td>
<td>Store at or below 25°C (10 mg/ml)</td>
</tr>
<tr>
<td></td>
<td>2°C – 8°C (10% solution)</td>
</tr>
<tr>
<td>Additional Manufacturer Instructions</td>
<td>Protect from light</td>
</tr>
<tr>
<td></td>
<td>Keep covered in carton till use</td>
</tr>
<tr>
<td>Recommendation by other studies</td>
<td>The National Center for Biotechnology Information recommends that when phenylephrine is diluted in</td>
</tr>
</tbody>
</table>
5% dextrose it will be stable for 48 hours at a pH of 3.5 – 7.5.\textsuperscript{14}

It cautions against prolonged exposure of phenylephrine to air or strong light as it may cause oxidation and discolouration.\textsuperscript{14}

**Phenylephrine when diluted in 0, 9% sodium chloride and stored at room temperature is physically and chemically stable for 60 days.\textsuperscript{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 \textmu g/ml and 400 \textmu g/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>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>1000 U/ml, 5000 U/ml (4ml ampoule)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>Fresenius Kabi</td>
</tr>
<tr>
<td>Manufacturer Recommended</td>
<td></td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>Below 25\textdegree C</td>
</tr>
<tr>
<td>Additional Manufacturer</td>
<td></td>
</tr>
<tr>
<td>Instructions</td>
<td>Do not freeze</td>
</tr>
</tbody>
</table>

No recommendations by other studies were found.
Table 7: Oxytocin package insert information and additional temperature storage recommendations by published studies.

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Oxytocic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>10 IU/ml (1 ml ampoule)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>Specpharm</td>
</tr>
<tr>
<td>Manufacturer Recommended</td>
<td></td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>2ºC – 8ºC</td>
</tr>
<tr>
<td>Additional Manufacturer</td>
<td>Do not freeze</td>
</tr>
<tr>
<td>Instructions</td>
<td>Do not remove ampoule from carton until use</td>
</tr>
<tr>
<td></td>
<td>Protect from direct sunlight</td>
</tr>
<tr>
<td>Recommendation by other studies</td>
<td>-5ºC to -20ºC up to 7 days.14</td>
</tr>
</tbody>
</table>

In this study by Nassata et al. oxytocin ampoules were stored at temperatures -5ºC and -20ºC for 7 days with a control stored at 4ºC. 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.

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Oxytocic Ergometrine maleate and oxytocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>Syntometrine® 500 micrograms/ml and oxytocin 5 IU/ml (1ml ampoule)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>Adcock Ingram Critical Care (Pty) Ltd</td>
</tr>
<tr>
<td>Manufacturer Recommended</td>
<td></td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>2ºC – 8ºC</td>
</tr>
<tr>
<td>Additional Manufacturer</td>
<td>Do not freeze. Protect from light.</td>
</tr>
<tr>
<td>Instructions</td>
<td></td>
</tr>
</tbody>
</table>
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.\(^1\)

If no refrigerator is available the World Health Organisation regards storage of Syntometrine®, at room temperature to a maximum of 30°C, for a maximum of 3 months as acceptable.\(^1\)

---

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

<table>
<thead>
<tr>
<th>Pharmacological classification</th>
<th>Hypoglycaemic agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>100 U/ml (10ml vial)</td>
</tr>
<tr>
<td>Manufacturer / Distributor</td>
<td>Novo Nordisk A/S</td>
</tr>
<tr>
<td>Manufacturer Recommended</td>
<td></td>
</tr>
<tr>
<td>Storage Temperature</td>
<td>2°C – 8°C</td>
</tr>
<tr>
<td>Room temperature (maximum 25°C) for one month</td>
<td></td>
</tr>
<tr>
<td>Additional Manufacturer</td>
<td>Do not freeze</td>
</tr>
<tr>
<td>Instructions</td>
<td>Keep out of sunlight</td>
</tr>
<tr>
<td>Recommendation by other studies</td>
<td><strong>If no refrigerator is available then insulin can be stored at room temperature for up to 2 weeks.</strong>(^1)</td>
</tr>
</tbody>
</table>

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 25th day insulin tolerance test was performed on rabbits.

When insulin was stored at 32°C and 37°C 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.

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°C – 8°C 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°C – 8°C 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°C to 6°C 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. The iced gel pack decreases the Styrofoam® cooler box’s interior temperature and the insulation property of the Styrofoam® 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. 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.

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.
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. The methods recommended by WHO are summarised in the table below.

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

<table>
<thead>
<tr>
<th>Name of Unit</th>
<th>Description</th>
<th>Cold life (Temperature &lt; 10(^0)C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Boxes</td>
<td>Insulated container lined with frozen ice packs</td>
<td>Two to seven days at room temperature of up to 43(^0)C</td>
</tr>
<tr>
<td>Vaccine Carriers</td>
<td>Small insulated containers with frozen ice packs</td>
<td>18 to 50 hours at room temperature of up to 43(^0)C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjuncts</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Water-packs</td>
<td>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.</td>
</tr>
<tr>
<td>Foam pads</td>
<td>Sponge like, soft material placed on top of water packs inside a vaccine carrier allowing full closure of carrier lid.</td>
</tr>
</tbody>
</table>

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°C to 70°C and the manufacturer’s assurance of an accuracy of ±1°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 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*
References


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.

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Anaesthetic drug storage, temperature sensitive medication, passive refrigeration, anaesthetic drug stability, cold chain medicines
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Professor BJS. Diedericks – my mentor

Dr E. Turton – the Head of Department of Anaesthesiology

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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°C – 23,8°C with a median of 14,8°C. This method of drug storage was not effective to ensure optimal storage temperature for all temperature-sensitive anaesthetic drugs (requiring storage at 2°C – 8°C) on 235 temperature measurements (88% with a 95% Confidence Interval of 83,6% to 91,4%). The number and placement 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°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°C. 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°C – 8°C 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°C. 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.\textsuperscript{1} Incorrect storage conditions may result in accelerated degradation of drugs, loss of potency and adverse patient outcomes.\textsuperscript{2} It is therefore imperative that drugs used in anaesthesia are stored securely while remaining easily accessible for anaesthetic use in daily practice.\textsuperscript{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.\textsuperscript{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

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name (Manufacturer)</th>
<th>Concentration</th>
<th>Manufacturer recommendation</th>
<th>Published literature recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine chloride</td>
<td>Suxamethonium® (Fresenius Kabi, Bodene (Pty) Ltd)</td>
<td>100 mg / 2ml</td>
<td>2°C – 8°C</td>
<td>Room temperature for 4,8 months(^5), Room temperature (light resistant) for 2,8 months(^5)</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Rocuronium (Biotech Laboratories (Pty) Ltd)</td>
<td>50 mg / 5ml</td>
<td>2°C – 8°C</td>
<td>Storage in room temperature for 14 days lead to unfavourable intubating conditions(^7)</td>
</tr>
<tr>
<td>Atracurium</td>
<td>Atracurium (GlaxoSmithKline)</td>
<td>10 mg / ml</td>
<td>2°C – 8°C</td>
<td>Storage at room temperature for two weeks does not cause clinical significant drug degradation(^8)</td>
</tr>
<tr>
<td>Cis – Atracurium</td>
<td>Nimbex® (GlaxoSmithKline)</td>
<td>5 mg / 2ml</td>
<td>2°C – 8°C (Diluted solution can be stored at 5 – 25°C)</td>
<td>Room temperature (light resistant) for 3,8 months(^6)</td>
</tr>
<tr>
<td>Phenylepherine hydrochloride</td>
<td>Phenylepherine® (Biomedi S.A., Abbott)</td>
<td>10 mg / ml</td>
<td>At or below 25°C</td>
<td>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})</td>
</tr>
<tr>
<td>Phenylepherine hydrochloride</td>
<td>Minims Phenylepherine® (Soflens(Pty) Ltd )</td>
<td>50 mg / 0,5ml</td>
<td>2°C – 8°C (2,5% solution store below 25°C)</td>
<td>Room temperature (light resistant) for 3,8 months(^6)</td>
</tr>
<tr>
<td>Heparin</td>
<td>Heparin (Fresenius Kabi)</td>
<td>1000 U / ml, 5000 U / ml</td>
<td>Below 25°C</td>
<td>No recommendation by other studies</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Spec Oxytocin® (SpecPharm (Pty) Ltd)</td>
<td>10 U / ml</td>
<td>2°C – 8°C</td>
<td>Stored at -5°C to -20°C for 7 days (with five freeze thaw cycles) compared with storage at 4°C showed no difference in change on concentration(^11)</td>
</tr>
<tr>
<td>Ergometrine Maleate &amp; Oxytocin</td>
<td>Syntometrine® (Adcock Ingram (Pty) Ltd)</td>
<td>5U Oxytocin &amp; 0,5mg Ergometrine / ml</td>
<td>2°C – 8°C</td>
<td>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°C for a maximum of 3 months is acceptable(^12)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Actrapid HM® Novo Nordisk A/S</td>
<td>1000 U / 10ml</td>
<td>2°C – 8°C (Room temperature for one month)</td>
<td>Room temperature at 12 weeks(^13)</td>
</tr>
</tbody>
</table>
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. 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.

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](image)

A digital thermometer, Lasec SA (Pty) Ltd stock code: H3THE0062-000002, with a temperature measuring range of -20°C to 70°C and a manufacturer’s assurance of an accuracy of ±1°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.

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°C, maximum of 23.8°C with a median temperature value of 14.8°C.

![Cold drug storage unit temperature per theatre for the week](image)

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

In order for 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°C – 8°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°C – 8°C, 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°C, the above temperature range of adequacy was extended to 1°C – 9°C (from 2°C – 8°C). 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°C – 8°C). 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°C, median of 6.9°C and maximum of 8.5°C, only one temperature measurement was outside of the manufacturer’s recommended temperature storage range of 2°C – 8°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°C to 25.7°C (with a median of 22.4°C).

![Theatre Room Temperature](image)

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

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°C – 8°C) 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°C – 8°C (adequate for storage of temperature sensitive drugs) and more than 8°C (inadequate for storage of temperature sensitive drugs)

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

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°C – 8°C 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°C – 23.8°C with a median of 14.8°C 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°C – 8°C. 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 ±1°C 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°C (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°C – 8°C); two 15cm x 15cm 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°C – 8°C 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°C to a maximum decrease in 6.9°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. 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. 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.

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. 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°C for five to seven days), vaccine box (maintain temperature below 10°C for 18 – 50 hours) with adjuncts such as water packs and foam packs.

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°C 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°C – 8°C 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°C – 8°C. 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 guideline², 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°C – 8°C 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°C for an average of 4 hours and 30 minutes, up to 9 hours and 30 minutes, in a maximum theatre temperature of 25,7°C. 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*
References


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: 5

PROPRIETARY NAME AND DOSAGE FORM: Suxamethonium Chloride Fresenius 100 mg/2 ml
Injection

COMPOSITION: Each ml emulsion contains:
Active ingredient: Suxamethonium Chloride 100 mg
Sodium chloride 15 mg
Water for injection 2 ml

PHARMACOLOGICAL CLASSIFICATION: A1.7 (Paralyzing skeletal muscle relaxants).

PHARMACOLOGICAL ACTION: Suxamethonium chloride is a depolarizing, neuromuscular blocking agent. The index effect is to depolarize the membrane in the same manner as acetylcholine, but more persistently, which results in a brief period of time manifested by transient muscle fasciculations. This phase is followed by the neuromuscular paralysis, the reinnervation and finally the partial or complete recovery of the motor end plate.

INDICATIONS:
In surgical and obstetric conditions, including anesthesia, as an adjuvant to surgical anesthesia to facilitate 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 at least some of the components of Suxamethonium Chloride Fresenius.

WARNINGS AND SPECIAL PRECAUTIONS:
Suxamethonium Chloride Fresenius is contraindicated in patients with burns, those with antecedent symptoms of bronchospasm, asthma, severe asthma, or those with asthma with an unknown cause. Pulmonary edema, hypothyroidism, or hyperthyroidism should be avoided.

In patients with low serum potassium concentrations, suxamethonium may cause muscular fasciculation or muscle weakness.

The administration of Suxamethonium Chloride Fresenius may result in transient increases in heart rate and blood pressure. However, these effects are not considered to be clinically significant.

Suxamethonium Chloride Fresenius is contraindicated in patients with severe cardiovascular disease, including severe coronary artery disease, severe arrhythmias, and severe hypertension. Severe respiratory depression, severe allergic reactions, and severe anaphylactic reactions. These effects are not considered to be clinically significant.

DOSAGE AND ADMINISTRATION:
Suxamethonium Chloride Fresenius should be used with caution in patients with reduced pulmonary function activity as it may prolong succinylcholine-induced AED.

The volume of the dose should be limited to a maximum of 3 ml.

There have been reports of prolonged neuromuscular blockade following the use of Suxamethonium Chloride Fresenius. A repeat dose of Suxamethonium Chloride Fresenius within a short time (of the previous dose) may result in the development of muscle weakness.

Malignant hyperthermia may occur in patients receiving Suxamethonium Chloride Fresenius. Profound hyperthermia may occur in situations where there is an increased respiratory carbon dioxide output. Hypothermia, usually not occurring, but necessary, may be fatal. A rapid elevation in body temperature should be avoided.

INTERACTIONS:
Many drugs interact with Suxamethonium Chloride Fresenius. The effects on the dosage of a drug may be due to a direct effect on the neuromuscular transmission or an alteration of the activity of a drug.

Suxamethonium Chloride Fresenius may interact with the following substances to produce prolonged paralytic effects: aminosynthetic and oropharyngeal antibiotics including penicillin, cephalosporin, cloxacin, oxacillin, erythromycin, tetracyclines, chloramphenicol, and tetracyclines. Quinidine, quinidine glucuronide, quinidine sulfate, disopyramide, digoxin, desoxyn, disopyramide, trimethoprim, and sulindac.

Prolonged toxicity may result from the use of a drug that interacts with or inhibits the metabolism of Suxamethonium Chloride Fresenius.

The effects of digoxin may be enhanced by Suxamethonium Chloride Fresenius. In patients receiving digoxin, monitoring of the serum digoxin level is recommended.

Presence and dosage may enhance the neuromuscular blocking effect of Suxamethonium Chloride Fresenius. The effects of Suxamethonium Chloride Fresenius may be enhanced by anticholinergic drugs such as atropine. Administration of Suxamethonium Chloride Fresenius before or after the use of non-depolarizing muscle relaxants may cause a muscle fasciculation. Presence and dosage may enhance the neuromuscular blocking effect of Suxamethonium Chloride Fresenius. The effects of Suxamethonium Chloride Fresenius may be enhanced by anticholinergic drugs such as atropine.

Side effects:
Suxamethonium Chloride Fresenius may cause a transient rise in intraocular pressure.

DOSAGE AND DIRECTIONS FOR USE:
This product is intended for use in adults. The recommended dose is 1 or 2 mg/kg intravenously.

SIDE EFFECTS:
Respiratory system disorders:
Frecuencies unknown:
Hypersensitivity reactions. Suxamethonium Chloride Fresenius has been reported to cause bronchospasm.

Nervous system disorders:
Frecuencies unknown:
Profound neuromuscular blockade and apnea may occur in patients with low serum concentrations of phosphorus phosphate. Dosage should be increased in patients with low serum concentrations of phosphorusosphate.

The administration of Suxamethonium Chloride Fresenius may result in transient increases in heart rate and blood pressure. However, these effects are not considered to be clinically significant.

Wound healing disorders:
Frecuencies unknown:
A transient rise in intraocular pressure may occur secondary to abdominal muscle fasciculations. These effects are not considered to be clinically significant.

Gastrointestinal disorders:
Frecuencies unknown:
A transient rise in intraocular pressure may occur secondary to abdominal muscle fasciculations. These effects are not considered to be clinically significant.

Urinary system disorders:
Frecuencies unknown:
A transient rise in intraocular pressure may occur secondary to abdominal muscle fasciculations. These effects are not considered to be clinically significant.

Other disorders:
Frecuencies unknown:
A transient rise in intraocular pressure may occur secondary to abdominal muscle fasciculations. These effects are not considered to be clinically significant.

Dosage:
Suxamethonium Chloride Fresenius may cause a transient rise in intraocular pressure.

Presentation:
Suxamethonium Chloride Fresenius is supplied as a sterile aqueous solution for injection in multiple-dose vials.

STORAGE INSTRUCTIONS:
Store at 2-8°C (36-46°F) protected from light.

REGISTRATION NUMBER:
M359273

NMB AND BUSINESS ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION:

E-mail: info@medicallinks.com

Identity:
Suxamethonium chloride, 100 mg/2 ml injection.

Presentation:
Pack of 10 x 2 ml ampoules.

DATE OF ISSUE OF THIS PACKAGE INSERT:
Lebanon 25 November 2017

Prescription only Medicine (POM)

Analytical Report:

Nigeria: 00455004004903

Zimbabwe: 13 Chloroform and lime

Kenya: 14368, POM

Tanzania: 147 NOA-BOC, POM

Zambia: 26402, POM
The use of appropriate respiratory precautions is recommended for the induction of remission in the acute phase of the disease. Inhalation aerosol therapy has been shown to improve oxygenation and reduce the incidence of respiratory complications.

Inhalation aerosol therapy is generally administered through a nebulizer, which delivers a mist of medication directly to the lungs. The mist is inhaled through a mouthpiece or a mask, and the medication is inhaled directly into the airways.

Nebulizers are available in different types, including jet nebulizers, ultrasonic nebulizers, and mesh nebulizers. The choice of nebulizer depends on the medication and the patient's needs. Jet nebulizers are generally used for medications that require higher flow rates, while ultrasonic nebulizers are better suited for medications that require lower flow rates.

The mist should be delivered to the patient's airways at a comfortable and effective rate, typically ranging from 5 to 10 L/min. The flow rate should be adjusted to ensure that the medication is delivered promptly and effectively.

Inhalation aerosol therapy is generally well tolerated by patients, with minimal side effects. However, some patients may experience coughing, wheezing, or a sensation of throat irritation. These side effects are typically temporary and resolve when the therapy is stopped.

In conclusion, inhalation aerosol therapy is a valuable tool in the management of respiratory diseases. It offers several advantages, including improved drug delivery, reduced medication costs, and fewer side effects compared to other delivery methods.

References
1. National Jewish Medical and Research Center. (2021). Inhalation therapy. Available at: https://www.njmri.org/service/inhalation-therapy
TRACRIUM®

SCHEDULING STATUS: 1800000118588

PROPRIETARY NAME AND DOSAGE FORM:
TRACRIUM® Injection 2.5 ml (solution for injection)
TRACRIUM® Injection 5.0 ml (solution for injection)

Exipients: 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 hepatic or renal 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 intraocular 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 ADEQUATE FACILITIES MUST BE AVAILABLE FOR ENDOTRAECHAL INTUBATION AND ARTIFICIAL VENTILATION.

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. Reversal of 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-line 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. The maximum dose is 4 mg/kg. 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 reactivation. 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 twitch 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 of continuous infusion at rates of 0.3 to 0.6 mg/Kg/hr (0.005 to 0.01 mg/kg/min). Accurate dosage administration of the infusion may be achieved using a syringe driver or infusion pump. TRACRIUM is administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Infusion hypotension 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) 8 hours
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 infiltration 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 haemodilution, 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. TRACRUM has not triggered this syndrome.

TRACRUM 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
are 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, hypoxia,
encephalopathy, uremia). 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 TRACRUM and
a causal relationship has not been established.

INTERACTIONS:
The neuromuscular block produced by TRACRUM may be
increased by the concomitant use of inhalation
anaesthetics such as halothane, isoflurane and enflurane.
The neuromuscular block produced by TRACRUM may be
increased by the concomitant use of:
- antibiotics, including the aminoglycosides, polymyxins,
  spectinomycin, tetracyclines, iminomycin and
diamycin
- antiarrhythmic medicines: propranolol, calcium channel
  blockers, lignocaine, procainamide and quinidine
- diuretics: furosemide and possibly mercaptop, thiazide
diuretics and acetazolamide
- magnesium sulphate
- ketamine
- lithium salts
- ganglion blocking agents: trimethaphan, hexamethonium.

Certain medicines may aggravate or unmask latent
myasthenia gravis or actually induce a myasthenic syndrome.
Increased sensitivity to TRACRUM would be consequent on
such development. Such medicines include various antibiotics,
beta-blockers (propranolol, oxprenolol), antiarrhythmic
medicines (procainamide, quinidine), antihypertensive
medicines (clonauquine, 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 contraceptive therapy. The
administration of combinations of non-depolarising
neuromuscular blocking agents in conjunction with
TRACRUM may produce a degree of neuromuscular
blockade in excess of that which might be expected were
an equipotent total dose of TRACRUM 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-depolarising agents such as TRACRUM, 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. TRACRUM 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
TRACRUM is excreted into human milk.

DOSE AND DIRECTIONS FOR USE:
Use by Injection:
TRACRUM 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 TRACRUM.
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 OVERDOSE AND
PARTICULARS OF ITS TREATMENT:
Signs: Prolonged muscle paralysis and its
consequences are the main signs of overdose.
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 glycopyrrionate, 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 TRACRUM should be discarded
immediately after use.

REGISTRATION NUMBER:
TRACRUM Injection 2.5 ml: 4/17/1263
TRACRUM Injection 5.0 ml: 4/17/1210

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

DATE OF PUBLICATION OF THE PACKAGE INSERT:
27 August 1998

GDS-13

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Botswana
TRACRUM Injection 2.5 ml: Reg No. B9316845 S2
TRACRUM Injection 5.0 ml: Reg No. B9316851 S2

Namibia
TRACRUM Injection 2.5 ml: Reg No. 9017/100585 NS2
TRACRUM Injection 5.0 ml: Reg No. 9017/100586 NS2

Zimbabwe
TRACRUM Injection 2.5 ml: Reg No. 8411/31848 PP
TRACRUM Injection 5.0 ml: Reg No. 8411/31849 PP
NIMBEX®

INJECTION, 0.5 mL (2 mg) per injection

SCHEDULED NAME

PROPRIETARY NAME AND DOSAGE FORM

NIMBEX® (2 mg/mL) injection

NIMBEX® (0.5 mL) injection

COMPOSITION:

Each mL of solution contains: nimodipine tartrate 2 mg, sodium chloride 1 mg, and water for injections. The pH of each solution is adjusted to 5.0-7.0. Each NIMBEX injection contains 0.005 mg of benzyl alcohol per mL. Each NIMBEX solution contains benzyl alcohol 0.005 mg per mL, as the preservative.

PHARMACOLOGICAL CLASSIFICATION:

A15B05A05 (Dihydropyridine calcium channel blocker).

PHARMACODYNAMIC ACTIVITY:

NIMBEX® is a dihydropyridine calcium channel blocker and has calcium channel antagonist properties. It is a dihydropyridine, which has been shown to be effective in the treatment of various diseases, including cardiovascular disorders, neurodegenerative diseases, and chronic pain.

Dosage in elderly patients:

No dosage adjustment is required in elderly patients. The safety and efficacy of NIMBEX® have been studied in elderly patients, and no dosage adjustment is required.

Dosage in patients with renal impairment:

No dosage adjustment is required in patients with renal impairment. The safety and efficacy of NIMBEX® have been studied in patients with renal impairment, and no dosage adjustment is required.

Dosage in patients with hepatic impairment:

No dosage adjustment is required in patients with hepatic impairment. The safety and efficacy of NIMBEX® have been studied in patients with hepatic impairment, and no dosage adjustment is required.

Drug interactions:

NIMBEX® is not known to interact with other medications. However, if NIMBEX® is used concomitantly with other medications, it is recommended to monitor for any adverse effects or changes in the effectiveness of the medications.

Overdosage:

Overdosage of NIMBEX® is unlikely to occur. If overdose occurs, supportive measures should be initiated, such as monitoring and supportive care. There is no specific antidote for NIMBEX® overdose.

Adverse reactions:

NIMBEX® has been reported to cause headache, dizziness, flushing, and other side effects. These side effects are generally mild and transient. If severe side effects occur, discontinuation of the medication should be considered.

Dosage and administration

Use by intravenous bolus injection.

Dosage in adults:

Dose 1: 1.0 mg/kg
Dose 2: 0.5 mg/kg

The recommended initial dosage of NIMBEX® for adults is 1.0 mg/kg (0.5 mL per injection) administered by intravenous bolus injection. The dosage may be repeated if necessary. The maximum daily dosage is 6.0 mg/kg (3.0 mL per injection).

Drug interactions:

NIMBEX® is not known to interact with other medications. However, if NIMBEX® is used concomitantly with other medications, it is recommended to monitor for any adverse effects or changes in the effectiveness of the medications.

Overdosage:

Overdosage of NIMBEX® is unlikely to occur. If overdose occurs, supportive measures should be initiated, such as monitoring and supportive care. There is no specific antidote for NIMBEX® overdose.

Adverse reactions:

NIMBEX® has been reported to cause headache, dizziness, flushing, and other side effects. These side effects are generally mild and transient. If severe side effects occur, discontinuation of the medication should be considered.

Indications:

NIMBEX® is indicated for the treatment of patients with acute cerebrovascular disease, including acute ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage.

Contraindications:

NIMBEX® is contraindicated in patients with a known hypersensitivity to nimodipine or other dihydropyridine calcium channel blockers.

Warnings:

NIMBEX® should be used with caution in patients with cardiovascular disease, including patients with recent myocardial infarction, angina pectoris, and history of congestive heart failure. NIMBEX® should be used with caution in patients with renal impairment.

Precautions:

NIMBEX® should be used with caution in patients with a history of severe drug allergies. NIMBEX® should be used with caution in patients with a history of drug dependence. NIMBEX® should be used with caution in patients with a history of drug abuse.

Drug interactions:

NIMBEX® is not known to interact with other medications. However, if NIMBEX® is used concomitantly with other medications, it is recommended to monitor for any adverse effects or changes in the effectiveness of the medications.

Overdosage:

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<thead>
<tr>
<th>Issue/Injection Dose (mg/kg)</th>
<th>Anesthesia/Background</th>
<th>Time to 50% Suppression (min)</th>
<th>Time to Maximum Suppression (min)</th>
<th>Time to 25% Spontaneous Recovery (min)</th>
<th>Recovery Y (%) Recovery Time (min)</th>
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<td>NMBR</td>
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</tbody>
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**PEDIATRIC PATIENTS AGED 1 TO 12 YEARS:**

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</table>

**PRESCRIPTION:**

- Prescribing information is in accordance with the drug's label and must be read in conjunction with the drug's label and the prescribing information.

**STORAGE INSTRUCTIONS:**

- Store at 2°C to 8°C (36°F to 46°F). Do not freeze.

**RECOMMENDATIONS:**

- Administer at least 30 minutes before the procedure.

**SKILLS AND SIMILARITY:**

- Simular SKS 3 (0.5 mg/kg, 0.75 mg/kg) and SKS 4 (1 mg/kg, 1.5 mg/kg) have similar profiles.

**DATE OF ISSUE:**

- 2 November 1998

**NOTICE:**

- This product is intended for use in adult patients only.

**REFERENCES:**

- [Reference 1]

**AUTHOR:**

- John Doe

**AFFILIATION:**

- Department of Anesthesiology

**ACKNOWLEDGEMENTS:**

- Thank you to all contributors for their valuable input.

**DISCLAIMER:**

- The information provided is for educational purposes only.

**CONCLUSIONS:**

- The use of benzodiazepines in anesthetic practice is recommended for patients with a history of benzodiazepine dependency.
SCHEDULING STATUS: 5

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

COMPOSITION: Each 1 ml ampoule contains 5 mg of phenylephrine hydrochloride. Each 1 ml ampoule contains 5 mg of hydrocortisone sodium succinate. Use as an aqueous solution and add water for injection.

PHARMACOLOGICAL CLASSIFICATION: E.7.2.7 Vasoconstrictor. Comprises a sympathomimetic amines agent.

PHARMACOLOGICAL ACTION: Phenylephrine is a alpha-1-adrenergic receptor agonist. After injection, phenylephrine produces peripheral vasoconstriction and increases in intraocular pressure. It also produces minor bradycardia. Beta 1 adrenergic receptor agonists are significant.

Pharmacokinetic properties: Following an intravenous injection of phenylephrine hydrochloride, the effective half-life was approximately 6 minutes. The steady-state volume of distribution (Vss) was calculated by injecting a bolus volume by a factor of 5, suggesting a high distribution into certain organ compartments. The average total plasma clearance (Cl) at 46 minutes was close to one-third of the cardiac output. A mean half-life of 4 minutes is given. Phenylephrine is extensively metabolized in the liver, where the drug is converted to metabolites with a half-life of 17.6 minutes. The metabolites are excreted in the urine and are believed to be responsible for the observed pharmacological effects.

INDICATIONS: Phenylephrine hydrochloride injection is indicated for the following: to maintain systemic arterial pressure and to increase cardiac output; to achieve an increase in arterial pressure; to maintain a stable systemic arterial pressure; to increase cardiac output; to maintain a stable systemic arterial pressure; to prevent hypotension; and to maintain a stable systemic arterial pressure.

CONTRAINDICATIONS: Hypersensitivity to any of the components of phenylephrine hydrochloride injection or to any other sympathomimetic agents.

WARNINGS AND SPECIAL PRECAUTIONS: Vasoconstrictor effects may result in increased systemic arterial pressure. Do not give to patients with sinoatrial block or with aortic insufficiency.

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

DOSE AND DIRECTIONS FOR USE: General dosage information: Patients treated with phenylephrine hydrochloride injection should be monitored for the development of accelerated hypertension and/or tachycardia. The dosage should be adjusted to maintain a stable systemic arterial pressure and heart rate. The dosage should be increased gradually and cautiously to achieve the desired effect. The dosage should be decreased gradually and cautiously to achieve the desired effect.

INTERACTIONS: Phenylephrine hydrochloride injection may be used concomitantly with other agents that are vasoconstrictors and/or cardiac stimulants, such as adrenergic sympathomimetics, beta-adrenergic blockers, and calcium channel blockers. The combination of phenylephrine hydrochloride injection with other agents that are vasoconstrictors and/or cardiac stimulants may result in an increase in blood pressure and heart rate. Phenylephrine hydrochloride injection may be used concomitantly with other agents that are vasoconstrictors and/or cardiac stimulants, such as adrenergic sympathomimetics, beta-adrenergic blockers, and calcium channel blockers. The combination of phenylephrine hydrochloride injection with other agents that are vasoconstrictors and/or cardiac stimulants may result in an increase in blood pressure and heart rate.

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Preparing a 50mg/ml Solution of Bolus Intravenous Administration

For bolus intravenous administration, add 10 mg [1 ml] of a 10 mg/ml concentration of PHENYLPROPIAMINE HYDROCHLORIDE INJECTION to 100 ml of 0.9% Sodium Chloride Injection. Shake well. This will yield a final concentration of 50 mg/ml. Withdraw an appropriate dose from the 50 mg/ml solution prior to bolus intravenous administration of the diluted solution.

Pressurizing Solution for Continuous Intravenous Infusion

For continuous intravenous infusions, withdraw 10 mg [1 ml] of 10 mg/ml concentration of PHENYLPROPIAMINE HYDROCHLORIDE INJECTION to 500 ml of 0.9% Sodium Chloride Injection. This will yield a final concentration of 20 mg/ml. Withdraw an appropriate dose from the 20 mg/ml solution prior to bolus intravenous administration of the diluted solution.

Dosages for Perioperative Setting

In adult patients undergoing surgical procedures with either neuraxial anesthesia or general anesthesia:
- 50 mg to 200 mg by intravenous bolus administration. The most frequently reported intravenous dose is 50 mg or 100 mg.
- 0.5 mg/kg/h to 2 mg/kg/h by intravenous continuous infusion. Tolerated to blood pressure goal.

Dosage for Septic or Other Vasodilatory Shock

In adult patients with septic or other vasodilatory shock:
- 0.5 mg/kg/h to 2 mg/kg/h by intravenous continuous infusion, tolerated to blood pressure goal. Doses above 6 mg/kg/h do not show significant increment in blood pressure.

SIDE EFFECTS

PHENYLPROPIAMINE HYDROCHLORIDE INJECTION can cause side effects. PHENYLPROPIAMINE HYDROCHLORIDE INJECTION may cause a transient feeling of heat and coldness of the skin and a temporary sensation of warmth in the legs. Compromise of the injection may cause local necrosis (see “WARNINGS AND SPECIAL PRECAUTIONS”). Peripheral vasodilation, possibly leading to necrosis or gangrene, may occur with prolonged use of PHENYLPROPIAMINE HYDROCHLORIDE INJECTION in high doses or by doses in the presence of peripheral vasculature disease.

Cardiac disorders:
- Less frequent: Angina, arrhythmias, dysrythmia, hypotension, tachycardia, and ventricular dysrhythmias

Central nervous system disorders:
- Less frequent: Nervousness or restlessness, insomnia, paresthesias, nervousness, tension

Immunologic disorders:
- Less frequent: Hyperalgesia

Psychiatric disorders:
- Less frequent: Anxiety, restlessness, agitation, psychic state, confusion

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

Gastrointestinal disorders:
- Less frequent: Constipation, diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders:
- Less frequent: Sweating, flushing, skin blanching, photodermatitis, skin rash, exfoliation, dermatitis

Musculoskeletal and connective tissue disorders:
- Less frequent: Muscular weakness

Respiratory, thoracic and mediastinal disorders:
- Less frequent: Dyspnea, pulmonary edema

Local reactions:
- Less frequent: Allergic reactions

Known symptoms of overdose and particular of its treatment

Symptoms of overdose include headache, hypotension which may be severe, palpitations, nausea and vomiting. For effective hypertensive effects, the administration should be adjusted 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 medication may be administered.
THERAPEUTIC NAME AND DOSAGE FORM

**PARAXINE PHENYLPROPAMINE 2.5% (Fenzy)***

**PARAXINE PHENYLPROPAMINE HYDROCHLORIDE 10% (Fenzy)**

**PRINCIPAL INGREDIENTS:**
- Paraxine Phenylpropamine
- Sodium chloride
- Phenylephrine hydrochloride

**PRODUCT DESCRIPTION:**
- A 50 mg/ml solution for intravenous use.

**DOSAGE AND ADMINISTRATION:**
- For intravenous use only.
- Use aseptic technique to prepare the injection site.

**WARNINGS AND PRECAUTIONS:**
- Use with caution in patients with cardiovascular disease.
- Use with caution in patients with hypertension.
- Use with caution in patients with diabetes.
- Use with caution in patients with glaucoma.
- Use with caution in patients with known sensitivity to phenylephrine.

**SIDE EFFECTS:**
- Hypertension
- Dizziness
- Tachycardia
- Nausea
- Vomiting
- Blurred vision
- Headache

**INTERACTIONS:**
- Use with caution with other cardiovascular medications.

**REPRESENTATIONS AND MANUFACTURERS:**
- Schering Plough Ltd.
- Available in 50 mg/ml solution.

**REGISTRATION NUMBERS:**
- N0208768
- N0208769

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**
- Schering Plough Ltd.
- 254 High St.
- Eltham, Victoria 3136

**DATE OF REGISTRATION:**
- 23 June 1991

**DATE OF REGISTRATION:**
- 23 January 2017

**REGISTRATION NUMBER:**
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- N0208768
HOW TO RECEIVE HEPARIN SODIUM FRESNIUS

Filter the solution prior to administering the medicine. The filter size must not be more than 25 μm.

You will not be advised to give any Heparin Sodium Fresenius, it is to be given only by a healthcare professional, such as a doctor or pharmacist.

Heparin Sodium Fresenius, when administered, causes a delayed, low-risk reaction/infusion, which is treated with conventional anticoagulant therapy.

The agent should not be administered in the event of any of the following reactions after receiving Heparin Sodium Fresenius:

- Allergic skin reaction, pruritus, or dehiscence
- Any prolonged or uncontrolled bleeding
- Palpitations, or nausea in an arm or leg which could indicate a blood clot
- Tell your doctor in the event of any of the following reactions after receiving Heparin Sodium Fresenius:

SPECIAL CONSIDERATIONS

If you receive more Heparin Sodium Fresenius than what is recommended, it may cause bleeding in the event of any of the above reactions.

DOSE AND ADMINISTRATION

- Palpitations, or nausea in an arm or leg which could indicate a blood clot
- If you receive more Heparin Sodium Fresenius than what is recommended, it may cause bleeding in the event of any of the above reactions.

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SPECIAL CONSIDERATIONS

If you receive more Heparin Sodium Fresenius than what is recommended, it may cause bleeding in the event of any of the above reactions.
Scheduling status: 54
Proprietary name (and dosage form)
SPEC OXYTOCIN 10 I.U. Ampoule, SPEC OXYTOCIN 5 I.U. Ampoule

Composition
SPEC OXYTOCIN is available in 10 I.U. ampoules containing 0.5 mg oxytocin, 5 I.U. ampoules containing 0.25 mg oxytocin. SPEC OXYTOCIN contains 10 I.U. of oxytocin per 1 ml of ampoule containing 0.25 mg oxytocin.

Pharmacological action
The active principle of oxytocin injections is the synthetic polypeptide identical to oxytocin, a hormone released in the posterior pituitary lobe of the pituitary gland. Oxytocin exerts a uterotonic effect in the smooth muscle of the uterus, causing contraction and detrusor muscle during labor, and in the glandular portions of the breast during lactation. It also stimulates the release of milk from the breast into the mammary glands.

Indication of use
SPEC OXYTOCIN is used for the induction of labor and for the prevention of postpartum hemorrhage. It is not recommended for the induction of labor in cases of premature rupture of the membranes, cervical insufficiency, or severe cephalopelvic disproportion.

Method of use
SPEC OXYTOCIN is administered by intravenous injection of 0.1 to 0.4 ml (10 to 40 I.U. per ml) in a volume of 10 ml of a suitable diluent such as normal saline or 5% dextrose in water.

Precautions and warnings
SPEC OXYTOCIN should not be used in cases of (1) known or suspected hypersensitivity to oxytocin or any of its components, (2) severe cephalopelvic disproportion or other obstructive factors, (3) premature labor, (4) conditions associated with increased risk of maternal or fetal distress due to uterine hyperstimulation, or (5) conditions associated with increased risk of maternal or fetal death due to uterine hyperstimulation.

Adverse reactions
Adverse reactions to SPEC OXYTOCIN are rare but may include uterine hyperstimulation, fetal distress, maternal or fetal death due to uterine hyperstimulation, or other adverse reactions that may be associated with the use of oxytocin.

References

Date of publication of this package insert: August 2021.

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SYNDOMETRINE®
(Ampoule)

COMPOSITION:
Each 1 ml ampoule contains: 50 synthetic oxytocin and 105 mg ergometrine maleate. Glucose free.

PHARMACOLOGICAL CLASSIFICATION:
A32 Oxotropics

PHARMACOLOGICAL ACTION:
SYNDOMETRINE® combines the rapid action of oxytocin with the sustained chelotropic effect of ergometrine.

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

CONTRA-INDICATIONS:
Frequency, first stage of labour, second stage of labour before crowning of the head, primary or secondary uterine inertia, or a prolapsed uterus requiring repair as in patients of high parity or with a uterine scar from previous caesarean section, unexplained cerebral, placental or placental separation in delivery, premature dilatation of the foetal membranes, or evidence of fetal distress. Eclampsia, preeclampsia; sensitivity to any of the ingredients; hypothyroidism; cardiac disease.

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

Prevention and treatment of postpartum haemorrhage: Following expulsion of the placenta, 1 ml intramuscularly, or intravenously if uterine prison’s heavy intravenous injections should be given slowly.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
There has been reports of nausea, vomiting and abdominal pain. Hypertension has occurred after oral intravenous administration. Stenocardia has been reported. Ampules are contraindicated in patients with renal impairment, cardiac arrest, and polyneuritis, and urination and micturition may occur.

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

SYNDOMETRINE® should not be given in brief 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 SYNDOMETRINE®, 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 eclampsia. Interaction with halothane has been reported to diminish the effect of ergometrine maleate on the uterus. Care is necessary in patients being treated with antihypertensive agents, or who have received a monoamine oxidase inhibitor in conjunction with local anesthetics, in severe hypertension that has been stated to occur SYNDOMETRINE® should be given under full electric observation.

Intravenous injection should be given slowly to prevent lactic acidosis and hypertension.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT:
Tocolytic agents are non-selective sedatives. Oxytocin is a vasodilator. Intravenous injection, intense rubber, extended duration of soft tissue, severe hypertension, water retention and incontinence with edema and coma, fetal asystole, fetal hyatomyelia, fetal hydrops, and extrauterine death. Subarachnoid haemorrhage have occurred.

Overdose of ergometrine maleate may give rise to gastrointestinal disturbances, hyperpyretic, respiratory depression, hyperpyrexia and coma. The patient should be kept under close surveillance, fluids intake and output as well as electrolytes should be monitored.

IDENTIFICATION:
A clear, colorless solution with a faintish blue fluorescence in a 1 ml clear glass ampoule sealed with two blue-coloured rings attached to the ampoule.

PRESENTATION:
Carton of 5 ampoules of 1 ml.

STORAGE INSTRUCTIONS:
Store in a refrigerator at 1 to 6°C.
Do not freeze. Protect from light.
Do not remove from the outer container until required for use.

SYNDOMETRINE® AMPOULES SHOULD BE KIP UP OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:
4/19/1965

NAME AND BUSINESS ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION:
Adcock Ingram Critical Care (Pty) Ltd, 1 Sabian Road, Aeroton, Johannesburg, 1055.

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
Date approved by NCC: 10 March 2011
Last date amended: 26 Nov 2015
SYNDOMETRINE®, Alliance and devices are registered Trade Marks of Alliance Pharmaceuticals Limited
**C: Digital Thermometer**

**TL8001B**

---

**Quick Details**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of Origin:</td>
<td>Guangdong, China (Mainland)</td>
</tr>
<tr>
<td>Brand Name:</td>
<td>TLX</td>
</tr>
<tr>
<td>Usage:</td>
<td>Household</td>
</tr>
<tr>
<td>Measuring temperature range:</td>
<td>-20°C to 70°C (-4°F to 158°F)</td>
</tr>
<tr>
<td>Measuring humidity range:</td>
<td>10% to 90% TH</td>
</tr>
<tr>
<td>Resolution:</td>
<td>±0.1°C or ±0.1°F, ±1%RH</td>
</tr>
<tr>
<td>Selectable temperature unit:</td>
<td>C/F</td>
</tr>
<tr>
<td>Power supply:</td>
<td>1.5V</td>
</tr>
<tr>
<td>Key feature:</td>
<td>Max/Min memory</td>
</tr>
<tr>
<td>Net weight:</td>
<td>137g</td>
</tr>
</tbody>
</table>

---

**Model Number:** TL8001B  
Theory: Temperature Sensor

Accuracy: ±1°C (or ±2°F), ±5%RH

Display comfort level: comfort, wet or dry

Dimensions: 110*100*20mm
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

<table>
<thead>
<tr>
<th>Day of the Week</th>
<th>Temperature change</th>
<th>Fluctuation Δ°C</th>
<th>Change room temperature Δ°C</th>
<th>Storage</th>
<th>Gel Packs</th>
<th>Number of Ampoules change</th>
<th>Time</th>
<th>Theatre number</th>
<th>Theatre in Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>Increase</td>
<td>8.1</td>
<td>-0.5</td>
<td>Plastic container</td>
<td>*2ABT to †1AB</td>
<td>0</td>
<td>11:00 -13:00</td>
<td>10</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>-4.9</td>
<td>0.3</td>
<td>Plastic Container</td>
<td>2ABT</td>
<td>1</td>
<td>07:30 -09:00</td>
<td>10</td>
<td>Y</td>
</tr>
<tr>
<td>Tuesday</td>
<td>Increase</td>
<td>7.2</td>
<td>0.3</td>
<td>Cartoon/Plastic</td>
<td>2ABT</td>
<td>0</td>
<td>13:00 -15:00</td>
<td>3</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>-5.5</td>
<td>0.7</td>
<td>Cartoon/Plastic</td>
<td>1AB to 2ABT</td>
<td>1</td>
<td>11:00 -13:00</td>
<td>4</td>
<td>Y</td>
</tr>
<tr>
<td>Wednesday</td>
<td>Increase</td>
<td>1</td>
<td>0.5</td>
<td>Plastic container</td>
<td>2ABT</td>
<td>0</td>
<td>09:00 -11:00</td>
<td>8</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>-6.9</td>
<td>0.3</td>
<td>Plastic container</td>
<td>1AB to 2ABT</td>
<td>0</td>
<td>07:30 -09:00</td>
<td>8</td>
<td>N</td>
</tr>
<tr>
<td>Thursday</td>
<td>Increase</td>
<td>1.9</td>
<td>0</td>
<td>Plastic container</td>
<td>†1SB</td>
<td>0</td>
<td>13:00 -15:00</td>
<td>9</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>-2.6</td>
<td>0.5</td>
<td>Plastic container</td>
<td>1AB</td>
<td>4</td>
<td>07:30 -09:00</td>
<td>5</td>
<td>Y</td>
</tr>
<tr>
<td>Friday</td>
<td>Increase</td>
<td>6</td>
<td>0.6</td>
<td>Plastic Container</td>
<td>2ABT to 1AB</td>
<td>1</td>
<td>07:30 -09:00</td>
<td>10</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Decrease</td>
<td>-2.1</td>
<td>0.1</td>
<td>Plastic Container</td>
<td>2ABT</td>
<td>0</td>
<td>15:00 -17:00</td>
<td>4</td>
<td>Y</td>
</tr>
</tbody>
</table>

*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 $2^\circ$C – $8^\circ$C, 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 $2^\circ$C – $8^\circ$C, per theatre for the week.
F: Letter of approval from HSREC

Health Sciences Research Ethics Committee

64

Dear Dr Nadia Cloete

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

Principal Investigator: Dr Nadia Cloete

Department: Anaesthesiology Department (Blouberg 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.HSD2018/0235/2010

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; ICH/GCP E8 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: 051-401 7794/5 or email EthicsHfS@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

Tel: +27 (0)51 401 7794/7796 E: ethicsHfS@ufs.ac.za

Block D, Dean's Division, Room D104 | P.O. Box: Potchefstroom 2503 | Internal Port Box G49 | Bloemfontein 9300 | South Africa
G: Letter of approval from HSREC after minor amendments

Health Sciences Research Ethics Committee

03-Oct-2019

Dear Dr Nadia Cloete

Ethics Number: UFS-HSD2018/0254/3019

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@0005; Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 43 CFR 46; (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
Office of the Dean: Health Sciences
T: +27 (0)51 400 7790/7794 | E: ethicsfhs@ufs.ac.za
ERB 00006240 | REC 230/08.011 | IORG0003187 | FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 399 (Internal Post Box G-50) | Bloemfontein 9300 | South Africa
www.ufs.ac.za
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 assured 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 healthcmt@health.gov.za or scedvcp@health.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 into 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://hsnr.lux.org.za

Thank you for the above in order.

Kind Regards,

Dr D Motsau
HEAD: HEALTH
Date: 26/07/2018
To: Prof G Lamarche
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 refrigerant drugs in the theatre suite 1-11 during the day time theatre list at the following times: 07:30, 09:00, and 11:00, 13:00, 15:00 and 17:00 for five consecutive days.

No patient data will be collected for this 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

Main Theatre
Universitas Hospital
11/06/2018

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

[Signature]

MP Seekosil (PNB4)
Assistant Manager
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
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</tr>
</tbody>
</table>
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°C. 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°C

**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. 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.

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.

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.

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.
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°C to 6°C 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. 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°C to 70°C. This thermometer has the manufacturers’ assurance of an accuracy of ±1°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)

<table>
<thead>
<tr>
<th>Drug Name and Manufacturer</th>
<th>Pharmacological Classification</th>
<th>Manufacturer Recommended storage temperature</th>
<th>Additional Manufacturer instructions</th>
<th>Recommendation by other studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>Muscle Relaxant</td>
<td>2 – 8°C</td>
<td>Protect from light</td>
<td>Room temperature for 4.8 months&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>50mg/ml (2ml ampoule)</td>
<td></td>
<td></td>
<td></td>
<td>Room temperature (light resistant) for 2.8 months&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>Fresenius Kabi</em> <em>Bodene (Pty) Ltd</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Muscle Relaxant</td>
<td>2 – 8°C</td>
<td>Maximum storage 12 weeks not exceeding 30°C If out of cold storage not to return</td>
<td></td>
</tr>
<tr>
<td>10mg/ml (5ml) ampoule</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MSD (Pty) Ltd</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>Muscle Relaxant</td>
<td>2 – 8°C</td>
<td>Protect from light. Do not freeze</td>
<td></td>
</tr>
<tr>
<td>10mg/ml (2.5ml ampoule)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>GlaxoSmithKline</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cis – Atracurium</td>
<td>Muscle Relaxant</td>
<td>2 – 8°C</td>
<td>Protect from light. Do not freeze. Do not remove from outer carton till administration. Diluted solution can be stored at 5 -25°C</td>
<td>Room temperature (light resistant) for 3.8 months&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>2mg/ml (2.5mls ampoule)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>GlaxoSmithKline</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Vasopressor</td>
<td>2 – 25°C</td>
<td>Protect from light. Keep covered in carton till use</td>
<td></td>
</tr>
<tr>
<td>10mg/ml (1ml ampoule)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>Abbott</em></td>
<td></td>
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</tr>
<tr>
<td>Drug Name and Manufacturer</td>
<td>Pharmacological Classification</td>
<td>Manufacturer Recommended storage temperature</td>
<td>Additional Manufacturer instructions</td>
<td>Recommendation by other studies</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>-----------------------------------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant</td>
<td>Below 25 °C</td>
<td>Do not freeze</td>
<td></td>
</tr>
<tr>
<td>1000IU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5000IU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4ml vial)</td>
<td>Fresenius Kabi Manufacturing SA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Oxytocic</td>
<td>2 – 8 °C</td>
<td>Do not freeze</td>
<td>-5 °C to -20 °C for 7 days¹¹</td>
</tr>
<tr>
<td>10 IU/ml</td>
<td>Specpharm</td>
<td></td>
<td>Do not remove ampoule from carton until use. Protect from direct sunlight</td>
<td></td>
</tr>
<tr>
<td>(1ml ampoule)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Hypoglycaemic agent</td>
<td>2 – 8 °C</td>
<td>Do not freeze. Keep out of sunlight</td>
<td>Room temperature 2 weeks¹²</td>
</tr>
<tr>
<td>100u/ml</td>
<td>Novo Nordisk A/S</td>
<td>Room temperature (max 25 °C) for one month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10ml vial)</td>
<td></td>
<td></td>
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</tbody>
</table>
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 theatre 1-5 and 8-11 (old text: 1-11) by the researcher.

07:30: The ambient temperature of theatre 1-5 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.
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.
References


3: RCOA. Storage of Drugs in anaesthetic Rooms: Guidance on best practice from the RCoA and AAGBI. June 2016

4: Australian and New Zealand College of Anaesthetist. Guidelines for the safe management and use of medications in Anaesthesia 2017; PS51: 3


8: Dewachter P. Frozen succinylcholine: The danger of being overzealous with its cold storage. BJA 2016 Feb; 116(2): 299-300

9: Papiewski, J. How does a Styrofoam cooler keep things cold? 2017 April; www.sciencing.com


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
TRACRIUM®

SCHEDULING STATUS: 100000014958

PROPRIETARY NAME AND DOSAGE FORM:
TRACRIUM® Injection 2.5 ml (solution for injection)
TRACRIUM® Injection 5.0 ml (solution for injection)
Exciptents: benzoic sulphonic acid and water for injections.

COMPOSITION:
Each ampoule of 2.5 ml contains 2.5 mg atracurium besylate. Each ampoule of 5.0 ml contains 5.0 mg atracurium besylate.

PHARMACOLOGICAL CLASSIFICATION:
A 17.1 Peripherally-acting muscle relaxant.

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 liver or renal 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 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 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 whom potentiation of certain, non-depolarising agents has been noted.

Regarding 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 i.v. 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 doses 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 reactivation. Recovery from the and of complete neuromuscular block (full block) without use of neostigmine occurs in about 35 minutes as measured by restoration of the twitch 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 of a continuous infusion at rates of 0.3 to 0.6 mg/kg/hr (0.005 to 0.01 mg/kg/min). Dosage of the infusion of the infusion may be achieved using a syringe pump. TRACRIUM may be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypotension 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:

<table>
<thead>
<tr>
<th>Infusion Solution</th>
<th>Period of Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride Intravenous BP (0.9 % w/v)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Glucose Intravenous BP (5 % w/v)</td>
<td>8 hours</td>
</tr>
<tr>
<td>Ringers injection USP</td>
<td>8 hours</td>
</tr>
<tr>
<td>Sodium Chloride (0.18 % w/v) and Glucose (4 % w/v) Intravenous Infusion BP</td>
<td>8 hours</td>
</tr>
<tr>
<td>Composed Sodium Lactate Intravenous Infusion BP (Hartmann’s Solution)</td>
<td>4 hours</td>
</tr>
</tbody>
</table>

When diluted in these solutions to give atracurium concentrations of 0.5 mg/ml to 0.9 mg/ml, infusion 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 the administration be slowed. Patients with clinically significant cardiovascular disease may be more susceptible to the effects of postoperative 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 infusions may require changes with prolonged administration in the ICU. The effects of haemodilution, haemophiltration 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; TRACRUM has not triggered this syndrome. TRACRUM 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, hypoxia, encephalopathy, uremia). 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 corticosteroids. These events have been seen infrequently in association with TRACRUM and a causal relationship has not been established.

INTERACTIONS:
The neuromuscular block produced by TRACRUM may be increased by the concomitant use of inhalation anaesthetics such as halothane, isoflurane and enflurane. The neuromuscular block produced by TRACRUM 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 mercaptopurine, thiazide diuretics and acetazolamide
- magnesium sulphate
- ketamine
- lithium salts
- ganglion blocking agents: trimethaphan, hexamethonium.
Certain medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome: increased sensitivity to TRACRUM would be consequent on such development. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmic medicines (procainamide, quinidine), antiasthmatic 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 TRACRUM may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of TRACRUM administered. Any synergistic effect may vary between different medicines combinations. A depolarising muscle relaxant such as succinylcholine chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarizing agents such as TRACRUM, 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. TRACRUM 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 TRACRUM is excreted into human milk.

DOSE AND DIRECTIONS FOR USE:
Use by injection:
TRACRUM 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 TRACRUM.
Phenylephrine Injection B.P.®
Phenylephrine Hydrochloride

10 mg per ml

5 x 1ml ampoules
For subcutaneous or intramuscular injection or slow intravenous infusion.

FRIDGE
KEEP IN

Each ampoule contains a 1% w/v solution of Phenylephrine Hydrochloride B.P.
For use as directed by a practitioner
Store at 0-25°C. Protect from light
Keep out of the reach of children

For the Information of the Medical Profession

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, sensitivy 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.

DOSE AND METHOD OF ADMINISTRATION

Dose:
By subcutaneous or intramuscular injection. Phenylephrine Injection is equivalent to 5 mg of phenylephrine hydrochloride. 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 (Nov. '89)

[Abbott]

Botswana: B9301910
Namibia: S1
2012-7924
SCHEDULING STATUS

PROPRIETARY NAME 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

INDICATIONS
- Prevention of deep vein thrombosis in patients undergoing major surgery

CONTRAINDICATIONS
- Hypersensitivity to heparin, including heparin-induced thrombocytopenia
- Recent major bleeding

WARNINGS AND SPECIAL PRECAUTIONS
- Use with caution in patients with a history of major surgery, trauma, or infection

DOSAGE AND DIRECTIONS FOR USE
- Filter the solution prior to administering the medicine. The filter size must be no more than 50 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 in the patient.
- Always administer Heparin Sodium Fresenius from the ampoule or vial, according to the filter and discard appropriate


The filter is for SINGLE USE only.

INDICATIONS
Heparin Sodium Fresenius is used as an anticoagulant in surgical and other potentially thrombogenic conditions, but it is chiefly used in the treatment of deep vein thrombosis.

CONTRAINDICATIONS
- Hypersensitivity to heparin, including heparin-induced thrombocytopenia
- Recent major bleeding

WARNINGS AND SPECIAL PRECAUTIONS
- Use with caution in patients with a history of major surgery, trauma, or infection

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WARNINGS AND SPECIAL PRECAUTIONS
- Use with caution in patients with a history of major surgery, trauma, or infection

DOSAGE AND DIRECTIONS FOR USE
- Filter the solution prior to administering the medicine. The filter size must be no more than 50 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 in the patient.
- Always administer Heparin Sodium Fresenius from the ampoule or vial, according to the filter and discard appropriate


The filter is for SINGLE USE only.

INDICATIONS
Heparin Sodium Fresenius is used as an anticoagulant in surgical and other potentially thrombogenic conditions, but it is chiefly used in the treatment of deep vein thrombosis.

CONTRAINDICATIONS
- Hypersensitivity to heparin, including heparin-induced thrombocytopenia
- Recent major bleeding

WARNINGS AND SPECIAL PRECAUTIONS
- Use with caution in patients with a history of major surgery, trauma, or infection

DOSAGE AND DIRECTIONS FOR USE
- Filter the solution prior to administering the medicine. The filter size must be no more than 50 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 in the patient.
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The filter is for SINGLE USE only.

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Heparin Sodium Fresenius is used as an anticoagulant in surgical and other potentially thrombogenic conditions, but it is chiefly used in the treatment of deep vein thrombosis.

CONTRAINDICATIONS
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- Recent major bleeding

WARNINGS AND SPECIAL PRECAUTIONS
- Use with caution in patients with a history of major surgery, trauma, or infection

DOSAGE AND DIRECTIONS FOR USE
- Filter the solution prior to administering the medicine. The filter size must be no more than 50 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 in the patient.
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The filter is for SINGLE USE only.

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Heparin Sodium Fresenius is used as an anticoagulant in surgical and other potentially thrombogenic conditions, but it is chiefly used in the treatment of deep vein thrombosis.

CONTRAINDICATIONS
- Hypersensitivity to heparin, including heparin-induced thrombocytopenia
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- Always administer Heparin Sodium Fresenius from the ampoule or vial, according to the filter and discard appropriate


The filter is for SINGLE USE only.
HOW TO RECEIVE HEPARIN SODIUM FRESNEXUS

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

You will not be expected to give yourself Heparin Sodium Fresnexus. It will be given to you by a healthcare professional who is trained to do so.

Heparin Sodium Fresnexus may also be given by continuous infusion, whereby the Heparin Sodium Fresnexus is mixed with either a saline or 0.9% sodium chloride solution and given by either injection into your vein (this is called as an infusion). The rate of the infusion will depend on the amount of Heparin Sodium Fresnexus you are given.

Your doctor will decide what dose, how often and how long you will receive Heparin Sodium Fresnexus. This depends on your condition and other factors such as age, body mass index, condition and other medications being given at the same time.

If you receive more Heparin Sodium Fresnexus than you should:

Stop the administration and refer the patient to a healthcare professional who is trained in the treatment of bleeding episodes. If you cannot stop the bleeding:

If the bleeding continues:

There are many cases of severe bleeding in which surgery is required. You may need medical attention if:

- You have a history of bleeding disorders or if you have a family history of bleeding disorders.
- You are allergic to heparin or any other component of the medication.
- You have a history of thrombophilia.
- You have a history of or are at risk for developing deep vein thrombosis or pulmonary embolism.
- You have a history of bleeding in the brain.

PROLONGED, INTRAVENOUS ADMINISTRATION

If systemic side effects are not managed in this manner, you should inform your doctor or pharmacist.

STOPPING AND DISPOSING OF HEPARIN SODIUM FRESNEXUS

Store all medicines out of reach of children.

Heparin Sodium Fresnexus will be stored in the pharmacy or in the hospital wards at or below 20°C.

Unused portions of the injection should be discarded.

PRESENTATION OF HEPARIN SODIUM FRESNEXUS

The 1 ml glass ampoules, packed with a filter in containers of 10.

IDENTIFICATION OF HEPARIN SODIUM FRESNEXUS

The Heparin Sodium Fresnexus may be identified by the following description:

- Name of the manufacturer.
- The name of the active ingredient.
- The amount of the active ingredient.
- The strength of the active ingredient.
- The form of the active ingredient.
- The number of units of the active ingredient.
- The number of ampoules in a container.
- The expiry date.
- The batch number.

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd
6 Grand Road, Parow, 7600, Port Elizabeth, South Africa

DATE OF PUBLICATION

In Heparin Sodium Fresnexus

106
### SCHEDULING STATUS

| 6.5 |

### PROPRIETARY NAME AND DOSAGE FORM:

- NIMBEX® 1 mg/ml (5 ml) Injection
- NIMBEX® 2 mg/ml (5 ml) Injection
- NIMBEX® 4 Injection

### COMPOSITION:

Each 1 mg/ml NIMBEX® 2.5 mg/ml ampicillin sodium clavulanate 3.2 mg/ml, as the base. Each 2 mg/ml injection 4.4 mg/ml ampicillin sodium clavulanate 6.4 mg/ml, as the base. Each 4 mg/ml injection 8.8 mg/ml ampicillin sodium clavulanate 12.8 mg/ml, as the base.

### PHARMACOLOGICAL CLASSIFICATION:

- A 17.11 Peripherally acting module released.

### PHARMACOLOGICAL ACTION:

- **Cbct** (clavulanate-associates, non-expressing ampicillin-associated avian leukosis virus). Clavulanate becomes a biological agent of the clavulanate, the drug has been shown to be fungicidal to clavulanate-resistant microorganisms. The action of clavulanate is to inhibit clavulanase enzymes, such as penicillins or cephalosporins, which are beta-lactamase inhibitors. The beta-lactamase inhibitor is clavulanate, which is known for its ability to inhibit clavulanate-resistant bacteria.

### Pharmacokinetic properties:

Clavulanate resistance occurs in the treatment of pharyngitis and tonsillitis. Amoxicillin clavulanate has been administered parenterally iv or orally. Intravenous administration is not associated with the major side effects that are observed with oral amoxicillin clavulanate. Intravenous clavulanate is less effective than oral amoxicillin clavulanate.

### Pharmacokinetics in Adults:

The clavulanate dose should be administered 2 hours before the first dose is administered. The drug is not recommended for the treatment of penicillin-resistant staphylococci or enterococci. The clavulanate dose should be administered 1 hour before the first dose of the drug. The drug is not recommended for the treatment of penicillin-resistant staphylococci or enterococci.

### Pharmacokinetics in Patients with Renal Impairment:

There are no clinically important differences between the pharmacokineties of clavulanate in patients with and without renal failure and in healthy adult patients. The recovery of clavulanate is unchanged in the presence of renal failure.

### Pharmacokinetics in Patients with Acute Intensive Care Unit (ICU) Patients:

The pharmacokinetics of clavulanate is unchanged in the presence of renal failure and in healthy adult patients. The recovery of clavulanate is unchanged in the presence of renal failure.

### INTEGRETION:

NIMBEX® is indicated for use in patients with known or suspected infection due to the wide-spectrum ampicillin-resistant strains.
cat result in progressive prolongation of effect.

Spontaneous Recovery: Once spontaneous recovery from neuromuscular block is underway, the rate is determined by the NMBX level. During tidal (100% oxygen) ventilation, the recovery times from 50% to 95% are approximately 11 and 18 minutes, respectively. Recovery from intubation following NMBX administration is variable with standard doses of anticholinesterase agents. The mean times from 20% to 75% recovery and to full recovery recovery are approximately 4 and 11 minutes respectively, following administration of the reversal agent at an average of 15% T1 recovery.

Data in pediatric patients aged 1 month to 12 years:

Table: NMBX Injection dose (mg/kg) and (mg) 1.08, 1.15, 1.18

<table>
<thead>
<tr>
<th>NMBX Injection Dose</th>
<th>Anesthetic Background</th>
<th>Time to 75% Suppression (min)</th>
<th>Time to Maximum Suppression (min)</th>
<th>Time to 25% Spontaneous T1 Recovery (min)</th>
<th>Time to 25% T1 Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.08</td>
<td>Halothane</td>
<td>1.4</td>
<td>2.7</td>
<td>3.4</td>
<td>3.7</td>
</tr>
<tr>
<td>1.15</td>
<td>Propofol</td>
<td>1.4</td>
<td>2.9</td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

Injection dose: NMBX 1.08 mg/kg administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 130 seconds following injection of NMBX. 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 0.4 mg/kg may produce similar intubation conditions in pediatric patients aged 1 to 12 years, NMBX 1.15 or 1.18 mg/kg clinically effective duration, and a faster spontaneous recovery profile than those observed in adults under similar anesthetic conditions. Small differences in the pharmacodynamic profiles were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarised in the tables below.

Pediatric Patients aged 1 to 11 months:

Table: NMBX Injection dose (mg/kg) and (mg) 1.08, 1.15, 1.18

<table>
<thead>
<tr>
<th>NMBX Injection Dose</th>
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<td>1.4</td>
<td>2.9</td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

Inhalation may be expected to extend the clinically effective duration of action. The duration of action is under study, and it is anticipated that the effect may be prolonged under ketamine and/or nitrous oxide anesthesia. However, data from intubation studies during ketamine anesthesia, using concentrations of ketamine that were not adequate to cause surgical anesthesia, but tolerated by the patients, showed that the effect of NMBX was not significantly prolonged under ketamine anesthesia.

Dosage in adults and children aged 2 to 12 years:

Maintenance of neuromuscular block may be achieved by infusion of NMBX. Infusion of NMBX is a recommended 5 μg/kg/min (or 18 mg/kg/hr) recommended to restore 50% to 95% of baseline and 80% to 95% of baseline suppression following evidence of spontaneous recovery. After an initial period of stabilization of neuromuscular block, the dose is 2 μg/kg/min (0.03 to 0.2 mg/kg/hr) should be adequate to maintain block in the range in most patients. Maintenance of neuromuscular block may be achieved by infusions of anticholinesterase agents following administration of the reversal agent at an average of 15% T1 recovery.

Data in adults and children aged 2 to 12 years:

Table: NMBX Injection dose (mg/kg) and (mg) 1.08, 1.15, 1.18

<table>
<thead>
<tr>
<th>NMBX Injection Dose</th>
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<td>2.9</td>
<td>4.7</td>
<td></td>
</tr>
</tbody>
</table>

INSTRUCTIONS FOR OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Prolonged muscle paralysis and its consequences are expected to be the main issue of overdose with NMBX injection. Appropriate treatment is essential. The administration of anticholinesterase agents, such as neostigmine, may aid recovery from neuromuscular blockade. Recovery may be accelerated by the administration of anticholinesterase agents, such as neostigmine, to aid spontaneous recovery.

IDENTIFICATION:

A clear, pale yellow or green-yellow solution free from visible particulate matter.

PRESENTATION:

NMBX 1.08 mg/kg/0.1 ml ampoules, NMBX 1.15 mg/kg/0.1 ml ampoules, NMBX 1.18 mg/kg/0.1 ml ampoules, NMBX 1.08 mg/kg/0.2 ml ampoules, NMBX 1.18 mg/kg/0.2 ml ampoules, NMBX 1.5 mg/kg/0.2 ml ampoules, NMBX 2.0 mg/kg/0.2 ml ampoules.

STORAGE INSTRUCTIONS:

Unopened ampoules: Store at room temperature. Do not freeze. After reconstitution, the solution should be used within 5 days. This product is marketed as a single dose ampoule and any unused portion of the solution must be discarded.

REGISTRATION NUMBER:

NMBX 1.08 mg/kg/0.1 ml ampoules: A1/17/15954
NMBX 1.15 mg/kg/0.1 ml ampoules: 717/17/144
NMBX 1.18 mg/kg/0.1 ml ampoules: 717/17/145
NMBX 1.5 mg/kg/0.2 ml ampoules: 9/11/12/208
NMBX 2.0 mg/kg/0.2 ml ampoules: 9/11/12/209

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

GlaxoSmithKline Hong Kong Ltd
498 Kwun Tong Industrial Estate, Kwun Tong, Kowloon

GATE OF PUBLICATION OF THE PACKAGING:

20 November 1989

GSK GlaxoSmithKline
### SPEC OXYTOCIN 10 I.U. Ampoule, SPEC OXYTOCIN 5 I.U. Ampoule

#### Composition
- SPEC OXYTOCIN 10 is available in 10 ampoules containing 10.0 (± 0.10) mg oxytocin base. Each milliliter contains 100 I.U. of oxytocin.
- SPEC OXYTOCIN 5 is available in 10 ampoules containing 5.0 (± 0.10) mg oxytocin base. Each milliliter contains 50 I.U. of oxytocin.

#### Pharmacological Characteristics
- **Pharmacologic action:** The active principle of oxytocin injection is a synthetic polypeptide identical to natural oxytocin, a hormone released by the posterior lobe of the pituitary. Oxytocin exercises a stimulating effect on the smooth muscles of the uterus, particularly towards the end of pregnancy, during labor, 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 slow intravenous infusion, oxytocin generally produces uterine contraction that are rhythmic, of increasing intensity, and from the first observed during stimulation.
- Oxytocin also produces a strong natriuretic effect. A dose of oxytocin does not cause uterine bleeding, but may cause an increase in the plasma sodium concentration and a decrease in the plasma renin activity.

### 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).
- Establishment of labour in cases of uterine inertia.
- During caesarean section, when delivering the child.

### Contraindications
- Requirement or enhancement of labour.

### Precautions
- **SPEC OXYTOCIN should be administered as an intravenous drip infusion preferably by means of a variable speed infusion pump.**
- A minimum of 100 I.U. of oxytocin is required for the equivalent of 100 I.U. of oxytocin. If the patient is unconscious, the dose of oxytocin should be increased by an additional 100 I.U. and the infusion rate should be increased by at least 20% of the initial rate. The total dose of oxytocin should not exceed 100 I.U.

### Administration of the drug
- **SPEC OXYTOCIN should be administered as a bolus injection together with an intravenous drip infusion.**
- The initial dose of 10 I.U. should be given as a bolus injection over a period of 15 minutes, followed by an intravenous drip infusion of 10 I.U. per hour.
- The rate of infusion should be increased or decreased as necessary to achieve the desired effect.
- The total dose of oxytocin should not exceed 100 I.U.
- **SPEC OXYTOCIN should be used with caution in patients with cardiac disease, hypertension, or diabetes mellitus.**

### Adverse Effects
- **SPEC OXYTOCIN is generally well tolerated.**
- However, occasionally, patients may experience headache, flushing, and nausea.

### References
- Additional information can be found in the manufacturer's instructions for use.

### Additional Information
- **SPEC OXYTOCIN should not be administered in the presence of cardiac disease, hypertension, or diabetes mellitus.**
- **SPEC OXYTOCIN should be administered as a bolus injection together with an intravenous drip infusion.**
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### Summary
- **SPEC OXYTOCIN is generally well tolerated.**
- However, occasionally, patients may experience headache, flushing, and nausea.

### Additional Information
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- **SPEC OXYTOCIN should be used with caution in patients with cardiac disease, hypertension, or diabetes mellitus.**

### Notes
- Additional information can be found in the manufacturer's instructions for use.
Actrapid® HM (ge)

Scheduling status: S

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

Composition:
Each 1 mL of solution contains insulin human soluble (insulin human soluble) provided by the following batch: 0.10 U/mL, 100 USP units/mL. The solution contains 90% monomeric insulin, preserved with 0.01% phenol.

Pharmacological classification:
A 21.1 (Hum) Insulin.

Pharmacological action:
Pharmacodynamic properties:
Actrapid® HM (ge) is a fast-acting soluble insulin.

Regulation: Administration of insulin is required for the treatment of diabetes mellitus. Insulin may be administered as a basal insulin, a basal-bolus insulin regimen, or in combination with other drugs, such as glucagon or sodium-glucose cotransporter (SGLT) inhibitors.

Pharmacokinetics:
Insulin in the human body is rapidly absorbed, reaching peak levels within 1 to 3 hours. The peak effect is observed at 3 to 5 hours following administration, and the duration of action is approximately 12 to 18 hours.

Distribution:
Insulin is distributed to the plasma and extravascular compartments. Distribution to the extravascular compartments is variable.

Indications:
Diabetes mellitus

Contraindications:
Hypersensitivity to human insulin or any of the excipients.

Warnings:
Inadequate dosage or discontinuation of treatment may result in hypoglycemia. In diabetic patients, symptoms of hypoglycemia include headache, pallor, tremors, dizziness, sweating, nausea, or vomiting. Severe hypoglycemia can lead to seizures, unconsciousness, and death. Insulin should be titrated cautiously in patients with impaired renal function or liver disease, as these conditions may affect insulin clearance. Persons with severe renal or hepatic impairment may require lower doses of insulin.

Adverse effects:
Adverse effects of insulin use include hypoglycemia, ketosis, and weight gain. Hypoglycemia is more common in patients with type 1 diabetes and those with a history of hypoglycemia.

Dosing and directions for use:
Dosing for each patient should be individualized and determined by the patient's clinical status, medical history, and individual response to treatment. The dose should be adjusted according to the clinical response and may be increased or decreased by 50% to 100% once daily.

Dosage:
The recommended dose of Actrapid® HM (ge) is 20 units of insulin per day. The dose should be titrated based on the patient's clinical response and may be increased or decreased by 50% to 100% once daily.

Pregnancy:
Actrapid® HM (ge) is a soluble insulin and is recommended for use during pregnancy. Pregnant patients should be monitored closely for signs of hypoglycemia, as the risk of hypoglycemia is increased during pregnancy.

Nursing:
Actrapid® HM (ge) is safe for use in lactating women. Breastfeeding women should be monitored closely for signs of hypoglycemia in infants.

Eye disorders:
Actrapid® HM (ge) is a soluble insulin and is not known to cause any specific ophthalmic complications. However, prolonged use of soluble insulin may result in ocular hypotony, which can lead to cataract formation.

Skin and subcutaneous disorders:
Actrapid® HM (ge) is a soluble insulin and is not known to cause any specific skin or subcutaneous complications. However, prolonged use of soluble insulin may result in subcutaneous lipodystrophy, which can lead to altered insulin absorption.

Known symptoms of overdose:
Symptoms of overdose may include severe hypoglycemia, which can be life-threatening. Hypoglycemia may be manifested by confusion, agitation, and seizures.

Side effects and special precautions:
Common side effects of soluble insulin include hypoglycemia, weight gain, and injection site reactions. Patients should be monitored closely for signs of hypoglycemia, as the risk of hypoglycemia is increased during pregnancy.

Special precautions:
Actrapid® HM (ge) is a soluble insulin and is not known to interact with other drugs, alcohol, or environmental factors. However, patients with a history of alcohol abuse or drug addiction should be monitored closely for signs of hypoglycemia.

Use in children:
Actrapid® HM (ge) is a soluble insulin and is not known to affect growth and development in children. However, children should be monitored closely for signs of hypoglycemia, as the risk of hypoglycemia is increased during pregnancy.

Use in the elderly:
Actrapid® HM (ge) is a soluble insulin and is not known to affect the pharmacokinetics or pharmacodynamics of insulin in elderly patients. However, prophylactic treatment with insulin may be required to prevent hypoglycemia in elderly patients with decreased renal function.

Interactions:
A number of interactions have been reported with other drugs that affect blood glucose levels.

Immune system disorders:
No specific immune system disorders associated with Actrapid® HM (ge) are known. However, patients with a history of severe allergic reactions to other drugs should be monitored closely for signs of hypoglycemia.

Drug interactions:
No specific drug interactions with Actrapid® HM (ge) are known. However, patients with a history of severe allergic reactions to other drugs should be monitored closely for signs of hypoglycemia.

Other interactions:
No specific interactions with Actrapid® HM (ge) are known. However, patients with a history of severe allergic reactions to other drugs should be monitored closely for signs of hypoglycemia.
Appendix D: Digital thermometer

**TL8001B**

![Digital Thermometer](image)

**Quick Details**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of Origin:</td>
<td>Guangdong, China (Mainland)</td>
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<tr>
<td><strong>Brand Name</strong>:</td>
<td>TLX</td>
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<tr>
<td><strong>Usage</strong>:</td>
<td>Household</td>
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<tr>
<td><strong>Measuring temperature range</strong>:</td>
<td>-20 °C to 70 °C (-58°F to 158°F)</td>
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<td><strong>Measuring humidity range</strong>:</td>
<td>10%~99%RH</td>
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<tr>
<td><strong>Resolution</strong>:</td>
<td>±0.1 °C (0.1°F) ±1%RH</td>
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<td>C/F</td>
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<tr>
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<tr>
<td><strong>Key feature</strong>:</td>
<td>Max/Min memory</td>
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<tr>
<td><strong>Model Number</strong>:</td>
<td>TL8001B</td>
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<tr>
<td><strong>Display comfort level</strong>:</td>
<td>Comfort, wet or dry</td>
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<tr>
<td><strong>Accuracy</strong>:</td>
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<td><strong>Dimensions</strong>:</td>
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<tr>
<td><strong>Theory</strong>:</td>
<td>Temperature Sensor</td>
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Appendix D: Digital Thermometer

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<tr>
<th>Account Number</th>
<th>Customer Order Number</th>
<th>Customer VAT Number</th>
<th>Qty</th>
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</table>

Sub Total: R 1,524.00
VAT @ 14%: R 213.36
Total incl. VAT: R 1,737.36

Attn: Nadia Cloete
Tel: 061 495 3907

Please see attached for the Special Terms and Conditions, and a link to Lasec SA’s Standard Terms and Conditions.
Appendix E: Data Capture Sheet

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<thead>
<tr>
<th></th>
<th>07:30</th>
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<tr>
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<td>Rocuronium</td>
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<td>Atracurium</td>
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<td>Cis-Atracurium</td>
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<td>Phenylephrine</td>
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<td>Heparin 1000U</td>
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<td>Heparin 5000U</td>
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<td>Insulin</td>
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<td>Oxytocin</td>
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Appendix F: Permission Letter Head of Department Anaesthesiology

Prof G Lamacraft
Acting Head of Department Anaesthesiology
University of Free State
Bloemfontein
10 April 2018

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

Matron P Seekoei  
Matron Universities Hospital Theatre  
Bloemfontein  
10 April 2018

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
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 $1^\circ$C).

**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.

<table>
<thead>
<tr>
<th>Date:</th>
<th>Theatre number:</th>
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<tbody>
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</tbody>
</table>

**Drug packaged**  
- Plastic container  
- Original carton  
- Loose

**Anaesthetic time**  
- Start:  
- End:  

<table>
<thead>
<tr>
<th></th>
<th>07:30</th>
<th>09:00</th>
<th>11:00</th>
<th>13:00</th>
<th>15:00</th>
<th>17:00</th>
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</thead>
<tbody>
<tr>
<td>Theatre Temp °C</td>
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<tr>
<td>Cooler Box Temp °C</td>
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</tbody>
</table>

**Amount of Drug Ampoules**  
- Suxamethonium  
- Rocuronium  
- Atracurium  
- Cis-Atracurium  
- Phenylephrine  
- Heparin 1000U  
- Heparin 5000U  
- Insulin  
- Oxytocin
Instructions for Authors

Thank you for choosing SAJAA in which to publish your paper.

Aims, scope and review policy: The Journal of Anaesthesia and Analgesia aims to publish original research and review articles of relevance and interest to the anaesthetists in academic, public sector and private practice. Papers are peer reviewed so that the contents are understandable, accurate, important, interesting and enjoyable.

SAJAA is indexed in EMBASE and it is accredited by the Department of Education for the measurement of research output of public higher institutions of South Africa (SAPHE accredited).

All manuscripts must be submitted online.

The online submission process will prompt authors to check off the following declarations:
1. This manuscript has not previously been submitted to SAJAA and has not been published previously.
2. No part of the work is original and all third party contributions (images, ideas and results) have been duly attributed to the originator(s).
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 convey with assign copyright to the South African Society of Anaesthetists (SAJAA).
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 included 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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1. Visit www.saja.co.za
2. Register on the website as an author and log in.
   - Click on Log in and log in with username and password if already registered.
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5. Follow the five steps to submit your paper.

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Case Studies: 1500-2500 words
Scientific Letters: 1000-1500 words
Letters to the Editor: 500-1000 words
Systematic Reviews in Anaesthesia: 2000-2500 words

Title page:
All articles must have a title page with the following information:
1. Title of the article.
2. Summary, methods, results, and conclusions.
3. Properly formatted abstracts in a structured format.
4. Keywords

Abstract:
All articles must include an abstract. The structured abstract for an original research article should be between 400 and 500 words and should consist of four paragraphs: Background, Methods, Results, and Conclusions.

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:
All references 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.

The style for references should follow the format set forth in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org) prepared by the International Committee of Medical Journal Editors. Abbreviations for journal titles should follow Index Medicus format. Authors are responsible for the accuracy of all references. Personal communications and unpublished data should not be referenced. If essential, such material should be incorporated in the appropriate place in the text.

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: Author(s) of document (if available), Title of document (if available), URL (Accessed Date).

The following are sample references:
1. Jun BK, Song SW, Park CS, Lee BH, Cho SK, Cho JH. The analysis of auxiliary sinus venation according to aging...
or other forms of conflict of interest, which may prevent them from executing and publishing unbiased research.

Conflict of interest

Authors must declare all financial contributions to their work...
N: Summary report: TurnitIn Plagiarism Search Engine

Dr PM van Zyl
Department of Pharmacology

14th January 2020

TO WHOM IT MAY CONCERN

DECLARATION ON PLAGIARISM

According to the University of the Free State’s Policy on the Prevention of Plagiarism and Dealing with Academic Writing Misconduct definition:

Plagiarism implies direct duplication of the formulation and insights of a source text with the intention of presenting it as one’s own work. Plagiarism cannot be confirmed as a result of mere similarities of words between the source text and the borrowed text as in the case of terminology, commonly used phrases and known facts. If plagiarism is suspected it must also be provable. The source text and borrowed text must therefore be placed side by side. The mere suspicion of plagiarism cannot form the basis of an accusation. Plagiarism is distinguished from forms of academic writing misconduct such as:

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- collusion and fabrication or falsification of data;
- deliberate dishonesty;
- purchasing assignments, dissertations and/or theses on the Internet and presenting such documents as one’s own work;
- presenting the same work for more than one course or in consecutive years; and
- the submission of another person’s work as one’s own original work.

To check for plagiarism the UFS uses software programmes like TURNITIN. The programme does not show plagiarism but rather focus on similarity in text against certain criteria.

The TURNITIN report on the mini-dissertation submitted by the candidate Nadia Cloete shows a 10% similarity. I am satisfied that when comparing the texts with the source documents it is evident that there is no plagiarism. Where text are similar it is properly referenced or quoted and referenced.

Regards
Dr PM van Zyl (supervisor)