PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

MUSCUDEX 100 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains sugammadex sodium equivalent to sugammadex 100 mg.

Excipient(s) with known effect

Contains up to 9,3 mg/mL sodium

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

MUSCUDEX solution for injection is a clear, colourless to slightly yellow-brown solution.

The pH is between 7 and 8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MUSCUDEX is indicated for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium.

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MUSCUDEX is also indicated for the immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

For the paediatric population, MUSCUDEX is only recommended for routine reversal of rocuronium induced blockade in children above 7 years of age.

4.2 Posology and method of administration

Posology

The recommended dose of MUSCUDEX depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen.

MUSCUDEX can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade.

Routine reversal of neuromuscular blockade

A dose of 4 mg/kg of MUSCUDEX is recommended if recovery has reached 1 to 2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade (see section 4.4).

A dose of 2 mg/kg of MUSCUDEX is only recommended if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium or vecuronium induced blockade (see section 4.4).

Immediate reversal

If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16 mg/kg of MUSCUDEX is recommended. There is no data to recommend the use of MUSCUDEX for immediate reversal following vecuronium induced blockade.

Special populations:

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Renal impairment

For mild and moderate renal impairment (creatinine clearance ≥ 30 and < 80 mL/min): The dose recommendations are the same as for adults without renal impairment. The use of MUSCUDEX in patients with severe renal impairment, including patients requiring dialysis (CrCl < 30 mL/min) is not recommended (see section 4.4).

Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of MUSCUDEX these patients.

Elderly patients

After administration of sugammadex as in MUSCUDEX at reappearance of T_2 following a rocuronium induced blockade, the median time to recovery of the T_4/T_1 ratio to 0,9 in adults (aged 18 to 64 years) was 2,2 minutes, in elderly adults (aged 65 to 74 years) it was 2,6 minutes and in very elderly adults (aged 75 years or more) it was 3,6 minutes. Even though the recovery times in the elderly tend to be slower, the same dose recommendation as for adults should be followed (see section 4.4).

Obese patients

In obese patients, the dose of MUSCUDEX should be based on actual body weight. The same dose recommendations as for adults should be followed.

Hepatic impairment

As MUSCUDEX is mainly excreted renally, no dose adjustments are required for patients with mild to moderate hepatic impairment.

Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of MUSCUDEX in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see section 4.4).

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Paediatric patients (under 7 years of age)

The data for the paediatric population are limited. There is insufficient information on the use of MUSCUDEX for children < 7 years of age. There is no information on MUSCUDEX use for neonates. The use of MUSCUDEX is therefore not recommended for use in these populations.

Children and adolescents (aged 7 to 17 years)

For reversal of rocuronium induced blockade at reappearance of T_2 in children and adolescents (7 to 17 years) 2 mg/kg of MUSCUDEX is recommended.

Immediate reversal in children and adolescents has not been investigated and is therefore not recommended.

MUSCUDEX 100 mg/ml may be diluted to 10 mg/mL to increase the accuracy of dosing in the paediatric population, 7 years and older.

Method of administration

MUSCUDEX should be administered under the supervision of an anaesthetist. MUSCUDEX should be administered intravenously as a single bolus injection. The bolus injection may be given rapidly, within 10 seconds, directly into a vein or into an existing IV line.

MUSCUDEX can be injected into the intravenous line of a running infusion with the following intravenous solutions:

Sodium chloride 9 mg/mL (0,9 %), glucose 50 mg/mL (5 %), sodium chloride 4,5 mg/mL (0,45 %) and glucose 25 mg/mL (2,5 %), Ringer's lactate solution, Ringer's solution, glucose 50 mg/mL (5 %) in sodium chloride 9 mg/mL (0,9 %).

For paediatric patients MUSCUDEX can be diluted using sodium chloride 9 mg/mL (0,9 %) to a concentration of 10 mg/mL.

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The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of the neuromuscular blockade. When certain medicines that may cause displacement interactions are administered parenterally within 7,5 hours of MUSCUDEX, patients should be monitored for signs of recurrence of neuromuscular blockade.

For instructions on dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

MUSCUDEX is contraindicated in patients with known hypersensitivity to sugammadex sodium or any of the excipients of MUSCUDEX (see section 6.1).

4.4 Special warnings and precautions for use

As is normal post-anaesthetic practice following neuromuscular blockade, it is recommended to monitor the patient in the immediate postoperative period for untoward events including recurrence of neuromuscular blockade.

MUSCUDEX is not to be used to reverse depolarising neuromuscular blocking medicines.

Waiting times for re-administration with neuromuscular blocking agents (NMBA) after reversal with MUSCUDEX.

Table 1: Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg sugammadex):

Minimum waiting time	NMBA and dose to be administered
5 minutes	1,2 mg/kg rocuronium

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4 hours	0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium

The onset of neuromuscular blockade may be prolonged up to approximately 4 minutes, and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes after re-administration of rocuronium 1,2 mg/kg within 30 minutes after sugammadex administration.

Based on PK modelling the recommended waiting time in patients with mild or moderate renal impairment for re-use of 0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium after routine reversal with sugammadex should be 24 hours. If a shorter waiting time is required, the rocuronium dose for a new neuromuscular blockade should be 1,2 mg/kg.

Re-administration of rocuronium or vecuronium after immediate reversal (16 mg/kg sugammadex):
For the very rare cases where this might be required, a waiting time of 24 hours is recommended.
If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking medicine should be used. The onset of a depolarising neuromuscular blocking medicine might be slower than expected, because a substantial fraction of postjunctional nicotinic receptors can still be occupied by the neuromuscular blocking medicine.

Medicine hypersensitivity

Medical practitioners should be prepared for the possibility of medicine hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions.

Renal impairment

MUSCUDEX is not recommended for use in patients with severe renal impairment, creatinine clearance < 30 mL/min, including requiring dialysis (see section 5.1 and section 5.2).

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Because of the estimated prolonged half-life of sugammadex in severe renally impaired patients, a full neuromuscular blockade may not be achieved after re-use of 0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium within 24 hours after sugammadex reversal.

Marked bradycardia

Marked bradycardia has been observed within minutes after the administration of sugammadex for reversal of neuromuscular blockade. Bradycardia may lead to cardiac arrest (see section 4.8). Patients should be closely monitored for haemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anticholinergic medicines such as atropine should be administered if clinically significant bradycardia is observed.

Monitoring respiratory function during recovery

Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular block. Even if recovery from neuromuscular blockade is complete, other medicines used in the peri- and postoperative period could depress respiratory function and therefore ventilatory support might still be required.
Should neuromuscular blockade re-occur following extubation, adequate ventilation should be provided.

Effect on haemostasis

In *in-vitro* experiments, additional aPTT and PT prolongation was noted for sugammadex in combination with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran.
In a study in volunteers, doses of 4 mg/kg and 16 mg/kg of sugammadex resulted in maximum mean prolongations of the activated partial thromboplastin time aPTT by 17 and 22 % respectively and

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prothrombin time international normalised ration of PT (INR) by 11 and 22 % respectively. These limited mean aPTT and PT(INR) prolongations were of short duration (≤ 30 minutes).

Based on the clinical database (n= 1 738) there was no clinically relevant effect of sugammadex alone or in combination with anticoagulants on the incidence of peri- or postoperative bleeding complications.

Since there is no information on the use of MUSCUDEX in patients with known coagulopathies, coagulation parameters should be carefully monitored according to routine clinical practice.

An increased risk of bleeding cannot be excluded in patients:

- with hereditary vitamin K dependent clotting factor deficiencies
- with pre-existing coagulopathies
- on coumarin derivates and at an INR above 3,5
- using anticoagulants who receive a dose of 16 mg/kg sugammadex.

If there is a medical need to give sugammadex as in MUSCUDEX to these patients, the anaesthesiologist needs to decide if the benefits outweigh the possible risk of bleeding complications, taking into consideration the patient's history of bleeding episodes and type of surgery scheduled. If MUSCUDEX is administered to these patients, monitoring of haemostasis and coagulation parameters is recommended.

Delayed recovery

Conditions associated with prolonged circulation time such as cardiovascular disease, old age (see section 4.2 for the time to recovery in elderly), or oedematous state (e.g. severe hepatic impairment) may be associated with longer recovery times.

Hepatic impairment

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MUSCUDEX is not metabolised nor excreted by the liver; therefore, dedicated studies in patients with hepatic impairment have not been conducted. Patients with severe hepatic impairment should be treated with great caution. Hepatic impairment may be accompanied by coagulopathy (see the information on the "***Effect on haemostasis***" above).

Light anaesthesia

When neuromuscular blockade was reversed intentionally in the middle of anaesthesia in clinical trials, signs of light anaesthesia were noted occasionally (movement, coughing, grimacing and suckling of the tracheal tube). If neuromuscular blockade is reversed, while anaesthesia is continued, additional doses of anaesthetic and/or opioid should be given as clinically indicated.

Use in intensive care unit (ICU)

MUSCUDEX has not been investigated in patients receiving rocuronium or vecuronium in the ICU setting.

Use for reversal of neuromuscular blocking medicines other than rocuronium or vecuronium

MUSCUDEX should not be used to reverse block induced by non-steroidal neuromuscular blocking medicines such as succinylcholine or benzylisoquinolinium compounds.

MUSCUDEX should not be used for reversal of neuromuscular blockage induced by steroidal neuromuscular blocking medicines other than rocuronium or vecuronium, since there are no efficacy and safety data for these situations. Limited data are available for reversal of pancuronium induced blockage, but it is advised not to use MUSCUDEX in this situation.

Recurrence of neuromuscular blockade

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The use of lower than recommended doses may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended (see section 4.2 and section 4.8).

4.5 Interactions with other medicines and other forms of interaction

The information reported in this section is based on the binding affinity between sugammadex, as contained in MUSCUDEX and other medicines, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking medicines and the pharmacokinetic interaction between neuromuscular blocking medicines and sugammadex.

Based on these data, no clinically significant pharmacodynamic interactions with other medicines are expected, with the exception of toremifene and fusidic acid - displacement interactions could not be excluded (no clinically relevant capturing interactions are expected); as well as hormonal contraceptives (no displacement interactions are expected).

Interactions potentially affecting the efficacy of sugammadex (displacement interactions)

Due to the administration of certain medicines after sugammadex, theoretically rocuronium or vecuronium could be displaced from MUSCUDEX. As a result, recurrence of neuromuscular blockade might be observed. In this situation the patient must be ventilated. Administration of the medicine which caused displacement should be stopped in case of an infusion. In situations when potential displacement interactions can be anticipated, patients should be carefully monitored for signs of recurrence of neuromuscular blockade (approximately up to 15 minutes) after parenteral administration of another medicine occurring within a period of 7,5 hours after MUSCUDEX administration.

Caution should be exercised when co-administering MUSCUDEX with the following medicines:

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Toremifene

For toremifene, which has a relatively high binding affinity constant for sugammadex and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with sugammadex, as contained in MUSCUDEX could occur.
The recovery of the train of four ratio, T_4/T_1, to 0,9 could therefore be delayed in patients who have received toremifene on the same day of surgery (see section 4.4).

Intravenous administration of fusidic acid

The use of fusidic acid in the pre-operative phase may cause some delay in the recovery of the T_4/T_1 ratio to 0,9.
No recurrence of neuromuscular blockade is expected in the postoperative phase, since the infusion rate of fusidic acid is over a period of several hours and the blood levels are cumulative over 2 to 3 days.

Interactions potentially affecting the efficacy of other medicines (capturing interactions):

Due to the administration of MUSCUDEX, certain medicines could become less effective due to a lowering of the (free) plasma concentrations. If such a situation is observed, the medical practitioner is advised to consider the re-administration of the medicine, the administration of a therapeutically equivalent medicine (preferably from a different chemical class) and/or non-pharmacological interventions as appropriate.

Hormonal contraceptives

In a simulation performed with a PK-PD model, it was found that the interaction between 4 mg/kg sugammadex and a progestogen could lead to a decrease in progestogen exposure (34 % of AUC) similar to the decrease seen when a daily dose of an oral contraceptive is taken 12 hours too late,

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which might lead to a reduction in effectiveness. Therefore, the administration of a bolus dose of MUSCUDEX is considered to be equivalent to one missed daily dose of oral contraceptive steroids (either combined or progestogen only).

Please refer to the missed dose advice in the professional information of the oral contraceptive, for any action required if an oral contraceptive is taken on the same day that MUSCUDEX is administered.

In the case of non-oral hormonal contraceptives, the patient must use an additional non hormonal contraceptive method for the next 7 days and refer to the advice in the package leaflet of the non-oral contraceptive.

Interactions due to the lasting effect of rocuronium or vecuronium

When medicines which potentiate neuromuscular blockade are used in the postoperative period, special attention should be paid to the possibility of recurrence of neuromuscular blockade. Please refer to the professional information of rocuronium or vecuronium for a list of the specific medicines which potentiate neuromuscular blockade. In case recurrence of neuromuscular blockade is observed, the patient may require mechanical ventilation and re-administration of MUSCUDEX (see section 4.2).

Interference with laboratory tests

In general, sugammadex as in MUSCUDEX does not interfere with laboratory tests. However, it has been shown to interfere with the serum progesterone assay.

This interference was observed in plasma samples spiked with a concentration of sugammadex in the same range as obtained for C_{max} after a dose of 16 mg/kg.

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In a study in volunteers, doses of 4 mg/kg and 16 mg/kg of sugammadex resulted in maximum mean prolongations of aPTT by 17 and 22 % respectively and of PT (INR) by 11 and 22 % respectively. These limited mean aPTT and PT (INR) prolongations were of short duration (≤ 30 minutes).
In *in-vitro* experiments a pharmacodynamic interaction (aPTT and PT prolongation) was noted with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran (see section 4.4).

Paediatric Population

No formal interaction studies have been performed. The above-mentioned interactions for adults and the warnings should also be taken into account for the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of MUSCUDEX has not been established in pregnant women.

For sugammadex no clinical data on exposed pregnancies are available.

Breastfeeding

Excretion of sugammadex in human milk has not been studied, but can be expected based on the pre-clinical data.

Caution should be exercised when administering MUSCUDEX to breastfeeding women.

Fertility

The effects of sugammadex on human fertility have not been investigated. Animal studies to evaluate fertility did not reveal harmful effects.

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4.7 Effects on ability to drive and use machines

MUSCUDEX has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

MUSCUDEX is administered concomitantly with neuromuscular blocking medicines and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess. The most frequently reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complications.

b. Tabulated summary of adverse reactions

System organ class	**Adverse reactions**
Immune system disorders	**Less frequent:** Medicine hypersensitivity reactions.
Injury, poisoning and procedural complications	**Frequent:** Prolonged neuromuscular blockade (with sub-optimal doses), airway complication of anaesthesia, (see section 4.4), procedural hypotension, procedural complication **Less frequent:** Anaesthetic complication
Respiratory, thoracic and mediastinal disorders	**Frequent:** Cough.
Nervous system disorders	**Frequent:** Dysgeusia

c. Description of selected adverse reactions

Anaesthetic complications

Anaesthetic complications, indicative of the restoration of neuromuscular function, include movement of a limb or the body or coughing during the anaesthetic procedure or during surgery, grimacing, or

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suckling on the endotracheal tube, and were judged to be related to treatment in about 1 % of the patients and in none of the placebo group. Most occurrences of anaesthetic complications were mild to moderate.

Procedural complication

Procedural complications included coughing, tachycardia, bradycardia, movement, and increase in heart rate.

Recurrence of neuromuscular blockade

The incidence of recurrence of neuromuscular blockade as measured with neuromuscular monitoring was 2 % after sugammadex and 0 % in the placebo group. Virtually all of these cases were from dose-finding studies in which a sub-optimal dose (< 2 mg/kg) was administered. In cases where recurrence of neuromuscular blockade is observed, the patient must be ventilated.

Medicine hypersensitivity reactions

Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers (for information on volunteers, see "***Information on healthy volunteers***" below).
These reactions varied from isolated skin reactions to serious systemic reactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to MUSCUDEX.
Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of tongue, swelling of the pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal.

Information on healthy volunteers

Hypersensitivity reactions, including anaphylaxis, have been observed with sugammadex. In a study in healthy conscious volunteers (placebo, n= 150; 4 mg/kg, n= 148; and 16 mg/kg, n= 150),

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hypersensitivity reactions were reported frequently with sugammadex 16 mg/kg and less frequently with sugammadex 4 mg/kg or placebo. In this study, dose dependent trends were also observed for dysgeusia, nausea and flushing.

Marked bradycardia

In post-marketing, cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex (see section 4.4).

Special populations

Pulmonary patients

In post-marketing data and in one dedicated clinical trial in patients with a history of pulmonary complications, bronchospasm was reported as a possibly related adverse event. As with all patients with a history of pulmonary complications, the medical practitioner should be aware of the possible occurrence of bronchospasm.

Morbidly obese patients

The adverse reaction profile in morbidly obese patients was generally similar to the profile in adult patients.

Paediatric population

The safety profile of sugammadex (up to 4 mg/kg) in paediatric patients above 7 years old, was similar to that in adults.

Airway complication of anaesthesia

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Airway complications of anaesthesia included bucking against the endotracheal tube, coughing, mild bucking, arousal reaction during surgery, coughing during the anaesthetic procedure or during surgery, or anaesthetic procedure-related spontaneous breath of patient.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Management of overdosage

MUSCUDEX can be removed using haemodialysis with a high-flux filter, but not with a low-flux filter. Based upon clinical studies, sugammadex concentrations in plasma are reduced with a high-flux filter by about 70 % after a 3 to 6-hour dialysis session.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

Pharmacotherapeutic group: all other therapeutic medicines, antidotes, ATC code: V03AB35

Mechanism of action

Sugammadex sodium injection is a modified gamma cyclodextrin. It is a selective relaxant binding medicine (SRBA) which forms a complex with the neuromuscular blocking medicines rocuronium and vecuronium in plasma, and it reduces the amount of neuromuscular blocking medicine available to bind

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to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium.

Pharmacodynamic effects

Sugammadex has been administered in doses ranging from 0,5 mg/kg to 16 mg/kg in dose response studies of rocuronium induced blockade (0,6, 0,9, 1,0 and 1,2 mg/kg rocuronium bromide with and without maintenance doses) and vecuronium induced blockade (0,1 mg/kg vecuronium bromide with or without maintenance doses) at different time points/depths of blockade. In these studies, a clear dose-response relationship was observed.

5.2 Pharmacokinetic properties

The sugammadex pharmacokinetic parameters were calculated from the total sum of non-complex-bound and complex-bound concentrations of sugammadex. Pharmacokinetic parameters such as clearance and volume of distribution are assumed to be the same for non-complex-bound and complex-bound sugammadex in anaesthetised patients.

Distribution

The observed steady-state volume of distribution of sugammadex sodium is approximately 11 to 14 litres in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Neither sugammadex nor the complex of sugammadex sodium and rocuronium bind to plasma proteins or erythrocytes, as was shown *in vitro* using male human plasma and whole blood. Sugammadex sodium exhibits linear kinetics in the dose range of 1 to 16 mg/kg when administered as an IV bolus dose.

Biotransformation

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No metabolites of sugammadex have been observed and only renal excretion of the unchanged medicine was observed as the route of elimination.

Elimination

In adult anaesthetised patients with normal renal function, the elimination half-life of sugammadex sodium is about 2 hours, and the estimated plasma clearance is about 84 mL/min. A mass balance study demonstrated that > 90 % of the dose was excreted within 24 hours. Ninety six percent (96 %) of the dose was excreted in urine, of which at least 95 % could be attributed to unchanged sugammadex. Excretion via faeces or expired air was < 0,02 % of the dose. Administration of sugammadex sodium to healthy volunteers resulted in increased renal elimination of rocuronium in complex.

Special populations:

Renal impairment and age

In a pharmacokinetic study comparing patients with severe renal impairment to patients with normal renal function, sugammadex levels in plasma were similar during the first hour after dosing and thereafter the levels decreased faster in the control group. Total exposure to sugammadex was prolonged, leading to approximately 17-fold higher exposure in patients with severe renal impairment. Low concentrations of sugammadex are detectable for at least 48 hours post-dose in patients with severe renal insufficiency.

In a second study, comparing subjects with moderate or severe renal impairment to subjects with normal renal function, sugammadex clearance progressively decreased and $t_{1/2}$ was progressively prolonged with declining renal function. Exposure was 2-fold and 5-fold higher in subjects with moderate and severe renal impairment, respectively. Sugammadex concentrations were no longer detectable beyond 7 days post-dose in subjects with severe renal insufficiency.

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Predicted pharmacokinetic parameters of sugammadex by age group and renal function based on compartmental modelling are presented below:

Selected patient characteristics				**Mean predicted PK parameters (CV %)**		
Demographics Age Body weight	Renal function Creatinine clearance (mL/min)			Clearance (mL/min)	Volume of distribution at steady state (L)	Elimination half-life (hr)
Adult	Normal		100	88 (22)	12	2 (21)
40 yrs	Impaired	Mild	50	51 (22)	13	4 (22)
75 kg		Moderate	30	31 (23)	14	6 (23)
		Severe	10	9 (22)	14	19 (24)
Elderly	Normal		80	75 (23)	12	2 (21)
75 yrs	Impaired	Mild	50	51 (24)	13	3 (22)
75 kg		Moderate	30	31 (23)	14	6 (23)
		Severe	10	9 (22)	14	19 (23)

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Adolescent	Normal		95	77 (23)	9	2 (22)
15 yrs	Impaired	Mild	48	44 (23)	10	3 (22)
56 kg		Moderate	29	27 (22)	10	5 (23)
		Severe	10	8 (21)	11	17 (23)
Child	Normal		51	37 (22)	4	2 (20)
7 yrs	Impaired	Mild	26	19 (22)	4	3 (22)
23 kg		Moderate	15	11 (22)	4	5 (22)
		Severe	5	3 (22)	5	20 (25)

Mean and coefficient of variation (CV in %) are presented. For Volume of distribution, no CV could be estimated from the model

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydrochloric acid (pH adjustment)
- Sodium hydroxide (pH adjustment)
- Water for injection

6.2 Incompatibilities

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This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Before mixing: 24 months

After first opening and dilution:

Chemical and physical in-use stability has been demonstrated for 48 hours at 2 °C to 25 °C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution and first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

MUSCUDEX solution for injection is packed in a type I colourless glass vial, sealed with a grey bromobutyl rubber stopper and with an aluminium flip-off cap.

MUSCUDEX is available in:

- 2 mL vials (200 mg/2 mL)
- 10 mL vials (500 mg/5 mL)

Pack sizes: 10 vials of 2 mL or 10 vials of 10 mL.

Not all pack-sizes may be marketed.

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6.6 Special precautions for disposal and other handling

MUSCUDEX can be injected into the intravenous line of a running infusion with the following intravenous solutions: sodium chloride 9 mg/mL (0,9 %), glucose 50 mg/mL (5 %), sodium chloride 4,5 mg/mL (0,45 %) and glucose 25 mg/mL (2,5 %), Ringers lactate solution, Ringers solution, glucose 50 mg/mL (5 %) in sodium chloride 9 mg/mL (0,9 %).

The infusion line should be adequately flushed (e.g., with 0,9 % sodium chloride) between administration of MUSCUDEX and other medicines.

Use in the paediatric population

For paediatric patients MUSCUDEX can be diluted using sodium chloride 9 mg/ml (0,9 %) to a concentration of 10 mg/mL.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

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Aeroton

Johannesburg

2013

Tel: +27 11 494 8000

8. REGISTRATION NUMBER(S)

59/34/0056

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 September 2024

10. DATE OF REVISION OF THE TEXT

Namibia: S3 Reg. No.: TBA

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