SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SUGAFLUX 100 mg/mL, Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains Sugammadex Sodium equivalent to Sugammadex 100 mg.

For the full list of excipients, (see section 6.1)

Sugar free.

3. PHARMACEUTICAL FORM

SUGAFLUX Injection:

Clear colourless to slightly yellow-brown solution filled in flint tubular vial fitted with rubber stopper and sealed with aluminium flip-off seal.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUGAFLUX is indicated for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium. SUGAFLUX is also indicated for the immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

For the paediatric population, SUGAFLUX 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

SUGAFLUX Injection should be administered under the supervision of an anaesthetist.

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 SUGAFLUX, patients should be monitored for signs of recurrence of neuromuscular blockade.

The recommended dose of SUGAFLUX depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen.
SUGAFLUX can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade.

Adults

Routine reversal of neuromuscular blockade

A dose of 4 mg/kg SUGAFLUX 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 SUGAFLUX 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 SUGAFLUX is recommended. There is no data to recommend the use of SUGAFLUX for immediate reversal following vecuronium induced blockade.

Special population

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 SUGAFLUX 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 SUGAFLUX in these patients.

Elderly patients

After administration of SUGAFLUX at the 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 (18 to 64 years) was 2,2 minutes, in elderly adults (65 to 74 years) it was 2,6 minutes and in very elderly adults (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 SUGAFLUX should be based on actual body weight. The same dose recommendations as for adults should be followed.

Hepatic impairment

For mild to moderate hepatic impairment: As SUGAFLUX is mainly excreted renally no dose adjustments are required.

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

Paediatric population

The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T_2). There is insufficient information on the use of SUGAFLUX for children < 7 years of age. There is no information on SUGAFLUX use for neonates. Therefore SUGAFLUX is not recommended for use in these populations.

Children and adolescents

For reversal of rocuronium induced blockade at reappearance of T_2 in children and adolescents (7 to 17

years) 2 mg/kg SUGAFLUX is recommended.

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

SUGAFLUX 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

SUGAFLUX Injection 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. SUGAFLUX has only been administered as a single bolus injection in clinical studies.

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

4.3 Contraindications

SUGAFLUX is contraindicated in patients with known hypersensitivity to sugammadex sodium or to any of the inactive ingredients (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 post-operative period for untoward events including recurrence of neuromuscular blockade.

Monitoring respiratory function during recovery:

Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following

reversal of neuromuscular blockade. Even if recovery from neuromuscular blockade is complete, other medicines used in the peri- and post-operative period could depress respiratory function and therefore ventilatory support might still be required.

Should neuromuscular blockade reoccur following extubation, adequate ventilation should be provided.

Recurrence of neuromuscular blockade:

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade, an incidence of 0,20 % was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence. 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).

Effect on haemostasis:

In a study 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 prothrombin time international normalized ratio [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 data-base and on a specific study in patients undergoing hip fracture/major joint replacement surgery there was no clinically relevant effect of sugammadex 4 mg/kg alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications.

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. In patients receiving

routine post-operative prophylactic anticoagulation this pharmacodynamic interaction is not clinically relevant. Since bleeding risk has not been studied systematically at higher doses than sugammadex 4 mg/kg, coagulation parameters should be carefully monitored according to routine clinical practice in patients with known coagulopathies and in patients using anticoagulants who receive a dose of 16 mg/kg sugammadex.

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 to these patients the anaesthesiologist needs to decide if the benefits outweigh the possible risk of bleeding complications taking into consideration the patients history of bleeding episodes and type of surgery scheduled. If sugammadex is administered to these patients monitoring of haemostasis and coagulation parameters is recommended.

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

Waiting times for re-administration with non-depolarising neuromuscular blocking medicines after reversal with sugammadex:

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

Minimum waiting time	**NMBA (non-depolarising neuromuscular blocking agents) and dose to be administered**
5 minutes	1,2 mg/kg rocuronium
4 minutes	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):

A waiting time of 24 hours is suggested. If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking medicine should be used. The onset of a depolarizing 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.

Renal impairment:

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

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.

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.

Marked bradycardia:

Marked bradycardia has been observed within minutes after the administration of sugammadex for reversal of neuromuscular blockade. Bradycardia may occasionally lead to cardiac arrest. (See section 4.8). Patients

should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anti-cholinergic medicines such as atropine should be administered if clinically significant bradycardia is observed.

Hepatic impairment:

Sugammadex 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. In case hepatic impairment is accompanied by coagulopathy see the information on the effect on haemostasis.

Use in Intensive Care Unit (ICU):

Sugammadex 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:

Sugammadex should not be used to reverse block induced by nonsteroidal neuromuscular blocking medicines such as succinylcholine or benzylisoquinolinium compounds.

Sugammadex should not be used for reversal of neuromuscular blockade 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 blockade, but it is advised not to use sugammadex in this situation.

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.

Drug hypersensitivity reactions:

Medical practitioners should be prepared for the possibility of medicine hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions (see section 4.8).

Sodium content:

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium- free'

4.5 Interaction with other medicines and other forms of interaction

The information in this section is based on binding affinity between sugammadex and other medicines, nonclinical 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 interaction with other medicines is expected, with exception of the following:
For toremifene and fusidic acid displacement interactions could not be excluded (no clinically relevant capturing interactions are expected).

For hormonal contraceptives a clinically relevant capturing interaction could not be excluded (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 sugammadex. 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 sugammadex administration.

Toremifene:

For toremifene, which has a relatively high binding affinity for sugammadex and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with sugammadex could occur. Medical practitioners should be aware that the recovery of the T_4/T_1 ratio to 0,9 could therefore be delayed in patients who have received toremifene on the same day of the operation.

Intravenous administration of fusidic acid:

The use of fusidic acid in the pre-operative phase may give some delay in the recovery of the T_4/T_1 ratio to 0,9. No recurrence of neuromuscular blockade is expected in the post-operative 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 sugammadex, 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:

The interaction between 4 mg/kg sugammadex and a progestogen was predicted to 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, which might lead to a reduction in effectiveness. For oestrogens, the effect is expected to be lower. Therefore the administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral contraceptive steroids (either combined or progestogen only). If sugammadex is administered at the same day as an oral contraceptive is taken reference is made to missed dose advice in the package leaflet of the oral contraceptive. In the case of

non-oral hormonal contraceptives, the patient must use an additional non hormonal contraceptive method for the next 7 days.

Interactions due to the lasting effect of rocuronium or vecuronium:

When medicines which potentiate neuromuscular blockade are used in the post-operative period special attention should be paid to the possibility of recurrence of neuromuscular blockade. Please refer to the package leaflet 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 sugammadex.

Interference with laboratory tests:

In general sugammadex does not interfere with laboratory tests, with the possible exception of 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.

In a study 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 in (section 4.4) should also be taken into account for the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnant women has not been established.

Breastfeeding

Excretion of sugammadex in human milk has not been studied but can be expected based on the pre-clinical data. Animal studies have shown excretion of sugammadex in breast milk. Caution should be exercised when administering SUGAFLUX to breastfeeding women.

4.7 Effects on ability to drive and use machines

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

Patients should not drive, use machinery or perform tasks that require concentration until they are certain that SUGAFLUX does not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

SUGAFLUX 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 complication (Frequent).

Adverse reactions are listed according to MedDRA primary system organ class. Within each system organ class, adverse reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Immune system

Less frequent: Medicine hypersensitivity reactions

Respiratory, thoracic and mediastinal disorders

Frequent: Cough

Nervous system disorders

Frequent: Dysgeusia

Injury, poisoning and procedural complications

Frequent: airway complication of anaesthesia, procedural hypotension, procedural complication, anaesthetic complication.

Description of selected adverse reactions

Medicine hypersensitivity reactions:

Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers (for information on volunteers, see Information on healthy volunteers below). In clinical trials of surgical patients, these reactions were reported less frequent and for post-marketing reports the frequency is unknown.

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 sugammadex.

Symptoms associated with these reactions can include flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal.

Airway complication of anaesthesia:

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.

Anaesthetic complication:

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 suckling on the endotracheal tube. (See section 4.4) light anaesthesia.

Procedural complication:

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

Marked bradycardia:

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

Recurrence of neuromuscular blockade:

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade, an incidence of 0,20 % was

observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence.

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.

In cases where recurrence of neuromuscular blockade is observed, the patient must be ventilated.

Information on healthy volunteers:

A study examined the incidence of drug hypersensitivity reactions in healthy volunteers given up to 3 doses of placebo, sugammadex 4 mg/kg or sugammadex 16 mg/kg. Reports of suspected hypersensitivity were adjudicated by a blinded committee. The incidence of adjudicated hypersensitivity was 1,3 %, 6,6 % and 9,5 % in the placebo, sugammadex 4 mg/kg and sugammadex 16 mg/kg groups, respectively. There were no reports of anaphylaxis after placebo or sugammadex 4 mg/kg. There was a single case of adjudicated anaphylaxis after the first dose of sugammadex 16 mg/kg (incidence 0,7 %). There was no evidence of increased frequency or severity of hypersensitivity with repeat dosing of sugammadex.

In a previous study of similar design, there were three adjudicated cases of anaphylaxis, all after sugammadex 16 mg/kg (incidence 2,0 %).

AEs considered frequent among subjects treated with sugammadex than in the placebo group, include dysgeusia (10,1 %), headache (6,7 %), nausea (5,6 %), urticaria (1,7 %), pruritus (1,7 %), dizziness (1,6 %), vomiting (1,2 %) and abdominal pain (1,0 %).

Other special population(s)

Pulmonary patients

In post-marketing data and in one dedicated study 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.

Paediatric population

A limited database suggests that the safety profile of sugammadex (up to 4 mg/kg) in paediatric patients above 7 years of age was similar to that in adults.

Morbidly obese patients

In one dedicated study in morbidly obese patients, the adverse reaction profile was generally similar to the profile in adult patients

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

SUGAFLUX can be removed using haemodialysis with a high-flux filter, but not with a low-flux filter. Based upon studies, SUGAFLUX 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

Pharmacotherapeutic group: All other therapeutic medicines, antidotes

ATC code: V03AB35

Pharmacological classification: A 34 Other

Mechanism of action

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

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 rocuronium bind to plasma proteins or erythrocytes. Sugammadex sodium exhibits linear kinetics in the dose range of 1 to 16 mg/kg when administered as an IV bolus dose.

Biotransformation

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 88 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 the increased renal elimination of rocuronium in the 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 t½ 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.

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	**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 75 kg	Impaired	Mild Moderate Severe	50 30 10	51 (22) 31 (23) 9 (22)	13 14 14	4 (22) 6 (23) 19 (24)
Elderly	Normal		80	75 (23)	12	2 (21)
75 yrs 75 kg	Impaired	Mild Moderate Severe	50 30 10	51 (24) 31 (23) 9 (22)	13 14 14	3 (22) 6 (23) 19 (23)
Adolescent	Normal		95	77 (23)	9	2 (22)
15 yrs 56 kg	Impaired	Mild Moderate Severe	48 29 10	44 (23) 27 (22) 8 (21)	10 10 11	3 (22) 5 (23) 17 (23)
Child	Normal		51	37 (22)	4	2 (20)
7 yrs 23 kg	Impaired	Mild Moderate Severe	26 15 5	19 (22) 11 (22) 3 (22)	4 4 5	3 (22) 5 (22) 20 (25)

*CV=coefficient of variation

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Sodium Hydroxide

Water for Injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in (section 6.6). Physical incompatibility has been reported with verapamil, ondansetron and ranitidine.

6.3 Shelf life

36 months

6.4 Special precautions for storage

SUGAFLUX:

Store at or below 25 °C. Protects from light (When not protected from light, the vial should be used within 5 days).

After first opening and dilution, chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 8 °C and 25 °C in below diluents

- 0,9 % Sodium Chloride
- 5 % Dextrose
- 0,45 % Sodium Chloride and 2,5 % Dextrose
- 5 % dextrose in 0,9 % sodium chloride
- Ringer's lactate solution

Keep the ampoules in the carton until required for use.

For storage conditions after the first opening of the medicine, (see section 6.3).

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of the container

SUGAFLUX Injection:

2R Clear treated USP Type I Glass Vial with a rubber stopper and a MM flip-off seal orange.

Pack sizes: 10 vials of 2 mL.

6.6 Special precautions for disposal and other handling

SUGAFLUX 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 SUGAFLUX and other medicines.

7. HOLDER OF CERTIFICATE OF REGISTRATION

RBC PHARMACEUTICALS (PTY) LTD.

23 Kiaat Street, ERF 926, Extension 7,

Noordwyk, Midrand, Gauteng,

South Africa, 1687

8. REGISTRATION NUMBERS

57/17.3/0572

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28th July 2026

10. DATE OF REVISION OF TEXT

TBA