

Approved Professional Information for Medicines for Human Use:

[PRODUCT NAME]

Please note: This application for registration is submitted as a duplicate and hence [PRODUCT NAME] is used in 1.3 to indicate the names as proposed:

Master (Proposed proprietary name)	Duplicate (Proposed proprietary name)
BREVISTELL IV	SUGAMMADEX IV AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

[PRODUCT NAME] 200 mg/2 mL Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains sugammadex sodium equivalent to 200 mg of sugammadex.

Each mL contains 108,8 g sugammadex sodium equivalent to 100 mg of sugammadex.

Sugar free.

Excipients with known effect: This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] is indicated for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium. [PRODUCT NAME] is also indicated for the immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. For the paediatric population, [PRODUCT NAME] 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

[PRODUCT NAME] should be administered under the supervision of an anaesthetist.

[PRODUCT NAME] 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.

[PRODUCT NAME] 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 [PRODUCT NAME] can be diluted using sodium chloride 9 mg/mL (0,9 %) to a concentration of 10 mg/mL.

[PRODUCT NAME] has only been administered as a single bolus injection in clinical trials.

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 [PRODUCT NAME], patients should be monitored for signs of recurrence of neuromuscular blockade.

The recommended dose of [PRODUCT NAME] depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen.

[PRODUCT NAME] 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 [PRODUCT NAME] 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 [PRODUCT NAME] is only recommended if spontaneous recovery has reached the reappearance of T₂, (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 [PRODUCT NAME] is recommended. There is no data to recommend the use of [PRODUCT NAME] for immediate reversal following vecuronium induced blockade.

Additional Information on 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 [PRODUCT NAME] 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 [PRODUCT NAME] in these patients.

Elderly Patients

After administration of [PRODUCT NAME] 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 (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 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 [PRODUCT NAME] 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 [PRODUCT NAME] 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 [PRODUCT NAME] in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see section 4.4).

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 [PRODUCT NAME] is recommended.

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

[PRODUCT NAME] 100 mg/mL may be diluted to 10 mg/mL to increase the accuracy of dosing

in the paediatric population, 7 years and older.

Paediatric population

The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T₂). There is insufficient information on the use of [PRODUCT NAME] for children < 7 years of age. There is no information on [PRODUCT NAME] use for neonates. Therefore [PRODUCT NAME] is not recommended for use in these populations.

4.3 Contraindications

- Hypersensitivity to the sugammadex or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

[PRODUCT NAME] is not to be used to reverse depolarising neuromuscular blocking agents.

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 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 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 (N=3,519) and on a specific study in 1184 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. Caution should be exercised when considering the use of [PRODUCT NAME] in patients receiving therapeutic anticoagulation for a pre-existing or co-morbid condition.

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 [PRODUCT NAME] is administered to these patients monitoring of haemostasis and coagulation parameters is recommended.

Waiting times for re-administration with neuromuscular blocking agents 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 and dose to be administered
5 minutes	1,2 mg/kg rocuronium
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 suggested.

If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking agent should be used. The onset of a depolarizing neuromuscular blocking agent might be slower than expected, because a substantial fraction of postjunctional nicotinic receptors can still be occupied by the neuromuscular blocking agent.

Renal impairment

[PRODUCT NAME] is not recommended for use in patients with severe renal impairment, 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

In rare instances, 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 agents other than rocuronium or vecuronium

[PRODUCT NAME] should not be used to reverse block induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.

[PRODUCT NAME] should not be used for reversal of neuromuscular blockade induced by steroidal neuromuscular blocking agents 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.

Medicine 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).

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, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking agents and the pharmacokinetic interaction between neuromuscular blocking agents and sugammadex. Based on these data, no clinically significant pharmacodynamic interaction with other medicinal products 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 T4/T1 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 T4/T1 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 2-3 days. For re-administration of sugammadex see section 4.2.

Interactions potentially affecting the efficacy of other medicinal products (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 estrogens, 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 [PRODUCT NAME] 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 and refer to the advice in the package leaflet of the product.

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 (see section 4.2).

Interference with laboratory tests

In general, sugammadex does not interfere with laboratory tests, with the possible exception of the serum progesterone assay. Interference with this test is observed at sugammadex plasma concentrations of 100 microgram/mL (peak plasma level following 8 mg/kg bolus injection).

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 (\leq 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.

Fertility

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

4.7 Effects on ability to drive and use machines

[PRODUCT NAME] has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

[PRODUCT NAME] is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess.

The frequently reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with sugammadex.

System Organ	Frequency		
Class	Frequent	Less Frequent	Not known
Immune system disorders		Medicine hypersensitivity reactions (see section 4.4)	
Respiratory, thoracic and mediastinal disorders	Cough		
Injury, poisoning and procedural	Airway complication of anaesthesia		

complications	Anaesthetic complication (see section 4.4) Procedural hypotension Procedural complication		
Nervous system disorders	Dysgeusia		

c. 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 uncommonly 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 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 (N=2,022), an incidence of 0,20 % was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence (see section 4.4).

Information on healthy volunteers:

A randomised, double-blind study examined the incidence of medicine 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 %).

In the Pooled Phase 1 database, AEs considered common ($\geq 1/100$ to $< 1/10$) or very common ($\geq 1/10$) and more frequent among subjects treated with sugammadex than in the placebo group, include dysgeusia, headache, nausea, urticaria, pruritus, dizziness, vomiting and abdominal pain.

Additional information on 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 physician 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 was similar to that in adults.

Morbidly obese patients

In one dedicated clinical trial in morbidly obese patients, the adverse reaction profile was generally similar to the profile in adult patients in pooled Phase 1 to 3 studies (see Table 2).

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 requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

[PRODUCT NAME] 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 by up to 70 % after a 3 to 6 hour dialysis session.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.34 Other

Pharmacotherapeutic group: all other therapeutic products, antidotes,

ATC Code: V03AB35

Sugammadex sodium injection is a modified cyclodextrin. It is a selective relaxant binding agent (SRBA) which forms a complex with the neuromuscular blocking agents rocuronium and vecuronium, and It reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium.

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 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.

Metabolism

No metabolites of sugammadex have been observed and only renal excretion of the unchanged product 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. Predicted pharmacokinetic parameters of sugammadex by age group and renal function based on compartmental modelling are presented below:

Selected patient characteristics			Predicted PK parameters		
Demographics	Renal function (creatinine clearance in mL/min)		Clearance in mL/min (CV)	Volume of distribution at steady state in litres	Elimination half-life in hours (CV)
Adult 40 yrs 75 kg	Normal	100	84 (22 %)	11,9	2,0 (19 %)
	Impaired	50	48 (22 %)	13,1	3,6 (19 %)
		30	29 (23 %)	13,7	6,1 (20 %)
		10	9 (19 %)	14,2	20,3 (20 %)
Elderly 75 yrs 75 kg	Normal	80	72 (26 %)	12,4	2,4 (23 %)
	Impaired	50	49 (22 %)	13,1	3,5 (19 %)
		30	29 (22 %)	13,7	6,1 (20 %)
		10	8 (19 %)	14,2	21,0 (23 %)
Adolescent 15 yrs 56 kg	Normal	95	76 (20 %)	9,3	1,7 (17%)
	Impaired	48	45 (24 %)	10,1	3,0 (21 %)
		29	26 (22 %)	10,5	5,2 (19 %)
		10	7 (18 %)	10,9	17,8 (18 %)
Child 7 yrs 23 kg	Normal	51	40 (21 %)	4,3	1,5 (16 %)
	Impaired	26	20 (20 %)	4,5	2,9 (19 %)
		15	11 (27 %)	4,6	5,2 (24 %)
		5	3 (22 %)	4,7	19,4 (23%)

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 (Inj. Grade) (pH adjuster)

Sodium Hydroxide (Inj. Grade) (pH adjuster)

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

Physical incompatibility has been reported with verapamil, ondansetron and ranitidine.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Keep the vial in the outer carton to protect from light.

After first opening and dilution, chemical and physical in-use stability has been demonstrated for 48 hours at 2 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

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

Austell Pharmaceuticals (Pty) Ltd, 560456, BREVISTELL IV, Solution for injection and 200 mg/2 mL

6.5 Nature and contents of container

[PRODUCT NAME] is available in 2 mL clear, glass vials sealed with chlorobutyl rubber stoppers sealed with flip-off aluminium seal, packed into cardboard cartons.

Pack sizes: 1's or 10's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG, 2193

Tel: +27 11 611 1400 or +27 860 287 835

8. REGISTRATION NUMBER

BREVISTELL IV 200 mg / 2 mL Solution for injection: 56/34/0456

SUGAMMADEX IV AUSTELL 200 mg / 2 mL Solution for injection: 56/34/0457.456

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 March 2024.

10. DATE OF REVISION OF THE TEXT