SUGAMMADEX SCIGEN Solution for injection 100 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

SUGAMMADEX SCIGEN solution for injection 100mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains sugammadex sodium equivalent to 100 mg sugammadex.
2 mL contains sugammadex sodium equivalent to 200 mg sugammadex.

For a full list of excipients, see section 6.1.

Excipient(s):
Each ml contains up to 9.5 mg sodium (see section 4.4).

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear and colourless to slightly yellow/brown solution free from visible particles.
The pH is between 7 and 8 and osmolality is between 300 and 500 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reversal of neuromuscular blockade induced by rocuronium or vecuronium in patients 2 years of age and older.

4.2 Posology and method of administration

Posology

Sugammadex should only be administered by, or under the supervision of an anaesthetist. The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of neuromuscular blockade
The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed.
The recommended dose does not depend on the anaesthetic regimen.
Sugammadex can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade:

Adults

Routine reversal:
A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T4/T1 ratio to 0.9 is around 3 minutes (see section 5.1).
A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 2 minutes (see section 5.1).

Using the recommended doses for routine reversal will result in a slightly faster median time to recovery of the T_4/T_1 ratio to 0.9 of rocuronium when compared to vecuronium induced neuromuscular blockade (see section 5.1).

Immediate reversal of rocuronium-induced blockade:
If there is a clinical need for immediate reversal following administration of rocuronium a dose of 16 mg/kg sugammadex is recommended. When 16 mg/kg sugammadex is administered 3 minutes after a bolus dose of 1.2 mg/kg rocuronium bromide, a median time to recovery of the T_4/T_1 ratio to 0.9 of approximately 1.5 minutes can be expected (see section 5.1).
There is no data to recommend the use of sugammadex for immediate reversal following vecuronium induced blockade.

Re-administration of sugammadex:
In the exceptional situation of recurrence of neuromuscular blockade post-operatively (see section 4.4) after an initial dose of 2 mg/kg or 4 mg/kg sugammadex, a repeat dose of 4 mg/kg sugammadex is recommended. Following a second dose of sugammadex, the patient should be closely monitored to ascertain sustained return of neuromuscular function.

Re-administration of rocuronium or vecuronium after sugammadex:
For waiting times for re-administration of rocuronium or vecuronium after reversal with sugammadex, see section 4.4.

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 sugammadex 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 sugammadex in these patients (see also section 5.1).

Elderly patients:
After administration of sugammadex 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 (18-64 years) was 2.2 minutes, in elderly adults (65-74 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, including morbidly obese patients, the dose of sugammadex 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 sugammadex 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 sugammadex in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see section 4.4).

Paediatric population

Children and adolescents (2 years and older):
SUGAMMADEX SCIGEN 100 mg/ml may be diluted to 10 mg/ml to increase the accuracy of dosing in the pediatric population (see section 6.6).

Routine reversal:
A dose of 4 mg/kg sugammadex is recommended for reversal of rocuronium or vecuronium induced blockade if recovery has reached at least 1-2 post-tetanic counts (PTC).
A dose of 2 mg/kg is recommended for reversal of rocuronium or vecuronium induced blockade at reappearance of T2 (see section 5.1).

Immediate reversal:
Immediate reversal in children and adolescents has not been investigated.

Term newborn infants and infants:
There is only limited experience with the use of sugammadex in infants (30 days to 2 years), and term newborn infants (less than 30 days) have not been studied. The use of sugammadex in term newborn infants and infants is therefore not recommended until further data become available.

Method of administration
Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, into an existing intravenous line (see section 6.6).
Sugammadex has only been administered as a single bolus injection in clinical trials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. (see section 6.1).

4.4 Special warnings and precautions for use

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 medicinal products used in the peri- and postoperative period could depress respiratory function and therefore ventilatory support might still be required.
Should neuromuscular blockade reoccur following extubation, adequate ventilation should be provided.

Effect on hemostasis:
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). Based on the clinical data-base (N=3519) there was no clinically relevant effect of sugammadex alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications.

In a specific study in 1184 surgical patients who were concomitantly treated with an anticoagulant, small and transient increases were observed in aPTT and PT(INR) associated with sugammadex 4 mg/kg, which did not translate into an increased bleeding risk with sugammadex compared with usual treatment.

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. Considering the transient nature of the limited prolongation of aPTT and PT caused by sugammadex alone or on top of these anticoagulants, it is unlikely that sugammadex has an increased risk of bleeding.

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.

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=2022), 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).

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

When rocuronium 1.2 mg/kg is administered within 30 minutes after reversal with sugammadex, the onset of neuromuscular blockade may be delayed up to approximately 4 minutes and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes.

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:
Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis (see section 5.1).

Interactions due to the lasting effect of rocuronium or vecuronium:
When medicinal products 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 medicinal products 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).

Potential interactions:

• Capturing interactions:
Due to the administration of sugammadex, certain medicinal products could become less effective due to a lowering of the (free) plasma concentrations (see section 4.5, hormonal contraceptives). If such a situation is observed, the clinician is advised to consider the re-administration of the medicinal product, the administration of a therapeutically equivalent medicinal product (preferably from a different chemical class) and/or non-pharmacological interventions as appropriate.

• Displacement interactions:
Due to the administration of certain medicinal products after sugammadex, theoretically rocuronium or vecuronium could be displaced from sugammadex. Displacement interactions are at present only expected for a few drug substances (toremifene and fusidic acid, see section 4.5). As a result recurrence of neuromuscular blockade might be observed. In this situation the patient must be ventilated. Administration of the medicinal product 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 medicinal product occurring within a period of 7.5 hours after sugammadex administration.

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. Isolated cases of bradycardia with cardiac arrest have been reported. (See section 4.8.) Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anti-cholinergic agents such as atropine should be administered if clinically significant bradycardia is observed.

Hepatic impairment:
Sugammadex is not metabolized 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 hemostasis.

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:
Sugammadex should not be used to reverse block induced by **nonsteroidal** neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.
Sugammadex 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 edematous state (e.g., severe hepatic impairment) may be associated with longer recovery times.

Drug hypersensitivity reactions:
Clinicians should be prepared for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions (see section 4.8).

Patients on a controlled sodium diet:
Each mL solution contains up to 9.5 mg sodium. A dose of 23 mg sodium is considered essentially 'sodium-free'. If more than 2.4 mL solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The information in this section is based on binding affinity between sugammadex and other medicinal products, 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 (see also section 4.4):
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. 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. However, 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.

Interactions potentially affecting the efficacy of other medicinal products (see also section 4.4):
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 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 and refer to the advice in the package leaflet of the product.

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 µg/mL.

Pediatric 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 pediatric population.

4.6 Pregnancy, and lactation

Pregnancy
For sugammadex no clinical data on exposed pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development.

Caution should be exercised when administering sugammadex to pregnant women.

Lactation:
It is unknown whether sugammadex is excreted in human breast milk. Animal studies have shown excretion of sugammadex in breast milk. Oral absorption of cyclodextrins in general is low and no effects on the suckling child are anticipated following a single dose to the breast-feeding woman.

Caution should be exercised when administering sugammadex to a breast-feeding woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of sugammadex has been evaluated in 3519 unique subjects across the Pooled Phase I-III safety database.

In the subset of Pooled Placebo-controlled trials where subjects received anesthesia and/or neuromuscular blocking agents (1078 subject exposures to sugammadex versus 544 to placebo), the following adverse events occurred in ≥ 2% of subjects treated with sugammadex and at least twice as often compared to placebo:

Table 2: Percent of Subject Exposures Receiving Anesthesia and/or Neuromuscular Blocking Agent in Pooled Phase I-III Placebo-Controlled Studies with Adverse Reactions Incidence ≥ 2% and at Least Twice As Often Compared to Placebo

System organ class	Adverse Reaction (Preferred Term)	Sugammadex (N=1078) %	Placebo (N=544) %
Injury, poisoning and procedural complications	Airway complication of Anaesthesia	4	0
	Anaesthetic complication	3	<1
	Procedural hypotension	3	2
	Procedural complication	2	1

Respiratory, thoracic and mediastinal disorders	Cough	5	2

Description of selected adverse reactions
In clinical studies, the investigator reported terms for complications resulting from anesthesia or surgery were grouped in the adverse event categories below, and included the following:

Complications resulting from anesthesia or surgery:

Airway Complication of Anesthesia:
Airway complications of anesthesia included bucking against the endotracheal tube, coughing, mild bucking, arousal reaction during surgery, coughing during the anesthetic procedure or during surgery, or contra breath (spontaneous breath of patient, anesthetic procedure related).

Anesthetic complication:
Anesthetic complications, indicative of the restoration of neuromuscular function, include movement of a limb or the body or coughing during the anesthetic procedure or during surgery, grimacing, or suckling on the endotracheal tube. (See section 4.4 light anesthesia.)

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

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).

Drug 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.

Information on healthy volunteers:
A randomized, double-blind study examined the incidence of drug hypersensitivity reactions in healthy volunteers given up to 3 doses of placebo (N=76), sugammadex 4 mg/kg (N=151) or sugammadex 16 mg/kg (N=148). 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%).
The most common adverse reaction in pooled healthy volunteers was dysgeusia (10%).

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).

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.

Pediatric population:
In studies of pediatric patients 2 to <17 years of age, the safety profile of sugammadex (up to 4 mg/kg) was generally similar to the profile observed in adults.

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

Patients with severe systemic disease:
In a trial in patients who were assessed as American Society of Anesthesiologists (ASA) Class 3 or 4 (patients with severe systemic disease or patients with severe systemic disease that is a constant threat to life), the safety profile in these ASA Class 3 and 4 patients was generally similar to that of adult patients in pooled Phase 1 to 3 studies (see Table 2). See section 5.1.

4.9 Overdose

In clinical studies, 1 case of an accidental overdose with 40 mg/kg was reported without any significant adverse reactions. In a human tolerance study sugammadex was administered in doses up to 96 mg/kg. No dose related adverse events nor serious adverse events were reported. Sugammadex can be removed using hemodialysis 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

Pharmacotherapeutic group: all other therapeutic products, ATC code: V03AB35

Mechanism of action:
Sugammadex is a modified gamma cyclodextrin which is a Selective Relaxant Binding Agent. It forms a complex with the neuromuscular blocking agents rocuronium or vecuronium in plasma and thereby 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 or 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.

Clinical efficacy and safety:
Sugammadex can be administered at several time points after administration of rocuronium or vecuronium bromide:

Routine reversal – deep neuromuscular blockade:
In a pivotal study patients were randomly assigned to the rocuronium or vecuronium group. After the last dose of rocuronium or vecuronium, at 1-2 PTCs, 4 mg/kg sugammadex or 70 mcg/kg neostigmine was administered in a randomised order. The time from start of administration of sugammadex or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was:

Table 3: Time (minutes) from administration of sugammadex or neostigmine at deep neuromuscular blockade (1-2 PTCs) after rocuronium or vecuronium to recovery of the T_4/T_1 ratio to 0.9

Neuromuscular blocking agent	Treatment regimen	
	Sugammadex (4mg/kg)	Neostigmine (70mcg/kg)
Rocuronium		
N	37	37
Median (minutes)	2.7	49.0
Range	1.2-16.1	13.3-145.7
Vecuronium		
N	47	36
Median (minutes)	3.3	49.9
Range	1.4-68.4	46.0-312.7

Routine reversal – moderate neuromuscular blockade:
In another pivotal study patients were randomly assigned to the rocuronium or vecuronium group. After the last dose of rocuronium or vecuronium, at the reappearance of T_2, 2mg/kg sugammadex or 50 mcg/kg neostigmine was administered in a randomised order. The time from start of administration of sugammadex or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was:

Table 4: Time (minutes) from administration of sugammadex or neostigmine at reappearance of T_2 after rocuronium or vecuronium to recovery of the T_4/T_1 ratio to 0.9

Neuromuscular blocking agent	Treatment regimen	
	Sugammadex (2mg/kg)	Neostigmine (50mcg/kg)
Rocuronium		
N	48	48
Median (minutes)	1.4	17.6
Range	0.9-5.4	3.7-106.9
Vecuronium		
N	48	45
Median (minutes)	2.1	18.9
Range	1.2-64.2	2.9-76.2

Reversal by sugammadex of the neuromuscular blockade induced by rocuronium was compared to the reversal by neostigmine of the neuromuscular blockade induced by cis-atracurium. At the reappearance of T_2 a dose of 2mg/kg sugammadex or 50 mcg/kg neostigmine was administered. Sugammadex provided faster reversal of neuromuscular blockade induced by rocuronium compared to neostigmine reversal of neuromuscular blockade induced by cis-atracurium:

Table 5: Time (minutes) from administration of sugammadex or neostigmine at reappearance of T_2 after rocuronium or cis-atracurium to recovery of the T_4/T_1 ratio to 0.9

Neuromuscular blocking agent	Treatment regimen

	Rocuronium and sugammadex (2mg/kg)	Cis-atracurium and neostigmine (50 mcg/kg)
N	34	39
Median (minutes)	1.9	7.2
Range	0.7-6.4	4.2-28.3

For immediate reversal:
The time to recovery from succinylcholine-induced neuromuscular blockade (1 mg/kg) was compared with sugammadex (16 mg/kg, 3 minutes later) – induced recovery from rocuronium-induced neuromuscular blockade (1.2 mg/kg).

Table 6: Time (minutes) from administration of rocuronium and sugammadex or succinylcholine to recovery of the T_1 10%

Neuromuscular blocking agent	Treatment regimen	
	Rocuronium and sugammadex (16mg/kg)	Succinylcholine (1mg/kg)
N	55	55
Median (minutes)	4.2	7.1
Range	3.5-7.7	3.7-10.5

In a pooled analysis the following recovery time for 16 mg/kg sugammadex after 1.2 mg/kg rocuronium bromide were reported:

Table 7: Time (minutes) from administration of sugammadex at 3 minutes after rocuronium to recovery of the T_4/T_1 ratio to 0.9, 0.8 or 0.7

	T_4/T_1 to 0.9	T_4/T_1 to 0.8	T_4/T_1 to 0.7
N	65	65	65
Median (minutes)	1.5	1.3	1.1
Range	0.5-14.3	0.5-6.2	0.5-3.3

Effects on QTc-interval:
In three dedicated clinical studies (N=287) sugammadex alone, sugammadex in combination with rocuronium or vecuronium and sugammadex in combination with propofol or sevoflurane was not associated with clinically relevant QT/QTc prolongation. The integrated ECG and adverse event results of Phase 2-3 studies support this conclusion.

Morbidly obese patients:
A trial of 188 patients who were diagnosed as morbidly obese (body mass index ≥ 40 kg/m2) investigated the time to recovery from moderate or deep neuromuscular blockade induced by rocuronium or vecuronium. Patients received 2 mg/kg or 4 mg/kg sugammadex, as appropriate for level of block, dosed according to either actual body weight or ideal body weight in random, double-blinded fashion. Pooled across depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio ≥ 0.9 in patients dosed by actual body weight (1.8 minutes) was statistically significantly faster ($p < 0.0001$) compared to patients dosed by ideal body weight (3.3 minutes).

Patients with severe systemic disease:
A trial of 331 patients who were assessed as ASA Class 3 or 4 investigated the incidence of treatment-emergent arrhythmias (sinus bradycardia, sinus tachycardia, or other cardiac arrhythmias) after administration of sugammadex.
In patients receiving sugammadex (2 mg/kg, 4 mg/kg, or 16 mg/kg), the incidence of treatment-emergent arrhythmias was generally similar to neostigmine (50 µg/kg up to 5 mg maximum dose) + glycopyrrolate (10 µg/kg up to 1 mg maximum dose). The percentage of patients with treatment-emergent sinus bradycardia was significantly lower (p=0.026) in the sugammadex 2 mg/kg group

compared with the neostigmine group. The percentage of patients with treatment-emergent sinus tachycardia was significantly lower in the sugammadex 2 mg/kg and 4 mg/kg groups compared with the neostigmine group (p=0.007 and 0.036, respectively). The safety profile in ASA Class 3 and 4 patients was generally similar to that of adult patients in pooled Phase 1 to 3 studies; therefore, no dosage adjustment is necessary. See section 4.8.

Pediatric Population:
A trial of 288 patients aged 2 to < 17 years of age, of which 276 patients received treatment (153 boys and 123 girls; ASA class 1, 2, and 3; 89.5% were Caucasian; median weight was 25 kg; median age was 7 years) investigated the safety and efficacy of sugammadex versus neostigmine as a reversal agent for neuromuscular blockade induced by rocuronium or vecuronium. Recovery from moderate block to a TOF ratio of ≥ 0.9 was significantly faster in the sugammadex 2 mg/kg group compared with the neostigmine group (geometric mean of 1.6 minutes for sugammadex 2 mg/kg and 7.5 minutes for neostigmine, ratio of geometric means 0.22, 95% CI (0.16, 0.32), (p<0.0001)). Sugammadex 4 mg/kg achieved reversal from deep block with a geometric mean of 2.0 minutes, similar to results observed in adults. These effects were consistent for all age cohorts studied (2 to < 6; 6 to < 12; 12 to < 17 years of age) and for both rocuronium and vecuronium. See section 4.2.

5.2 Pharmacokinetic properties

The sugammadex pharmacokinetic parameters were calculated from the total sum of non-complexbound 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 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 and rocuronium binds to plasma proteins or erythrocytes, as was shown in vitro using male human plasma and whole blood.
Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose.

Metabolism:
In preclinical and clinical studies 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 anaesthetized patients with normal renal function the elimination half-life ($t_{1/2}$) of sugammadex 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. 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 less than 0.02% of the dose. Administration of sugammadex 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 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.

A summary of sugammadex pharmacokinetic parameters stratified by age and renal function is presented below:

Table 8:

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	84 (22)	13	2 (22)
40 yrs 75 kg	Impaired	Mild Moderate Severe	50 30 10	47 (25) 28 (24) 8 (25)	14 14 15	4 (22) 7 (23) 24 (25)
Elderly	Normal		80	70 (24)	13	3 (21)
75 yrs 75 kg	Impaired	Mild Moderate Severe	50 30 10	46 (25) 28 (25) 8 (25)	14 14 15	4 (23) 7 (23) 24 (24)
Adolescent	Normal		95	72 (25)	10	2 (21)
15 yrs 56 kg	Impaired	Mild Moderate Severe	48 29 10	40 (24) 24 (24) 7 (25)	11 11 11	4 (23) 6 (24) 22 (25)
Middle childhood	Normal		60	40 (24)	5	2 (22)
9 yrs 29kg	Impaired	Mild Moderate Severe	30 18 6	21 (24) 12 (25) 3 (26)	6 6 6	4 (22) 7 (24) 25 (25)
Early childhood	Normal		39	24 (25)	3	2 (22)
4 yrs 16kg	Impaired	Mild Moderate Severe	19 12 4	11 (25) 6 (25) 2 (25)	3 3 3	4 (23) 7 (24) 28 (26)

CV=coefficient of variation

Pediatric Patients:
Sugammadex pharmacokinetic parameters were estimated in pediatric patients 2 to <17 years of age with patients enrolled into 3 age groups (2 to <6, 6 to <12 and 12 to <17 years of age) and intravenous doses of 2 or 4 mg/kg sugammadex administered for reversal of moderate or deep neuromuscular blockade, respectively. Both clearance and volume of distribution increase with increasing age in pediatric patients.

Sugammadex exposure ($AUC_{0\text{-}inf}$ and Cmax) increased in a dose-dependent, linear manner following administration of 2 and 4 mg/kg across patients 2 to <17 years of age. Sugammadex exposure was approximately 40% lower in patients 2 to <6 years of age following administration of 2 or 4 mg/kg sugammadex compared to older pediatric patients (6 to <17 years) and adults; however, this difference was not clinically relevant [see section 5.1].

The observed steady-state volume of distribution of sugammadex is approximately 3 to 10 liters and clearance is approximately 38 to 95 mL/min resulting in a half-life of approximately 1-2 hours in pediatric patients 2 to <17 years of age.

Gender:
No gender differences were observed.

Race:
In a study in healthy Japanese and Caucasian subjects no clinically relevant differences in pharmacokinetic parameters were observed. Limited data does not indicate differences in pharmacokinetic parameters in Black or African Americans.

Body weight:
Population pharmacokinetic analysis of adult and elderly patients showed no clinically relevant relationship of clearance and volume of distribution with body weight.

Obesity:
In one clinical study in morbidly obese patients, sugammadex 2 mg/kg and 4 mg/kg was dosed according to actual body weight (n=76) or ideal body weight (n=74). Sugammadex exposure increased in a dose-dependent, linear manner following administration according to actual body weight or ideal body weight. No clinically relevant differences in pharmacokinetic parameters were observed between morbidly obese patients and the general population.

5.3 Preclinical safety data

Carcinogenicity studies were not done given the intended single-dose use of sugammadex and given the absence of genotoxic potential.

Sugammadex did not impair male or female fertility in rats at 500 mg/kg/day representing approximately 6- to 50-fold greater systemic exposures as compared to human exposures at recommended dose levels. Further, no morphological alterations of male and female reproductive organs were noted in 4-week toxicity studies in rats and dogs. Sugammadex was not teratogenic in rat or rabbit.

Sugammadex is rapidly cleared in preclinical species, although residual sugammadex was observed in bone and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex does not adversely affect tooth colour or bone quality, bone structure, or bone metabolism. Sugammadex has no effects on fracture repair and remodelling of bone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid 3.7% and/or sodium hydroxide (to adjust pH)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Physical incompatibility has been reported with verapamil, ondansetron and ranitidine.

6.3 Shelf life

Refer to outer carton.

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 below 30°C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

2 mL of solution in type I glass vial closed with bromobutyl rubber stoppers with aluminium crimp-cap and flip-off seal.
Pack sizes: 10 vials of 2 mL

6.6 Special precautions for disposal and other handling

SUGAMMADEX SCIGEN 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 SUGAMMADEX SCIGEN and other drugs.

For pediatric patients SUGAMMADEX SCIGEN can be diluted using sodium chloride 9 mg/mL (0.9%) to a concentration of 10 mg/mL (see section 6.3).

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

7. PRODUCT REGISTRANT

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8. DATE OF REVISION OF THE TEXT

Jan 2024