1. **NAME OF THE MEDICINAL PRODUCT**

Sugamred 100 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:
Sugammadex sodium
Equivalent to
Sugammadex.....100mg

Excipient(s) with known effect:
Each ml solution contains up to 9.7 mg sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless to slightly yellow solution.
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 adults.

For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.

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 (see section 4.4).

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 T4/T1 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:
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).
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.

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 (body mass index ≥ 40 kg/m2), the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed.

Hepatic impairment:
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).
For mild to moderate hepatic impairment: as sugammadex is mainly excreted renally no dose adjustments are required.

Paediatric population

Children and adolescents (2 – 17 years):
[Invented name] 100 mg/ml may be diluted to 10 mg/ml to increase the accuracy of dosing in the paediatric population (see section 6.6).

Routine reversal:

A dose of 4 mg/kg sugammadex is recommended for reversal of rocuronium induced blockade if recovery has reached at least 1-2 PTC.
A dose of 2 mg/kg is recommended for reversal of rocuronium 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
[Invented name] 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 listed in 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 medicinal products 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 normalised 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 sugammadex in patients receiving therapeutic anticoagulation for a preexisting 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 sugammadex 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:
Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis (see section 5.1).

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 haemodynamic 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 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: 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 oedematous 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).

Sodium:
This medicinal product contains up to 9.7 mg sodium per ml, equivalent to 0.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 (displacement interactions):
Due to the administration of certain medicinal products 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 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.

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. Clinicians 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 2-3 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 medicinal products could become less effective due to a lowering of the (free) plasma concentrations. 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.

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 and refer to the advice in the package leaflet of the product.

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).

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 (≤ 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
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.

Breast-feeding
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 effect on the suckling child is anticipated following a single dose to the breast-feeding woman. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sugammadex therapy, taking into account the

benefit of breast feeding for the child and the benefit of therapy for the woman.

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

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

4.8 Undesirable effects

Summary of the safety profile

Sugammadex is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess. The most commonly reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication (Common (≥ 1/100 to < 1/10)).

Table 2: Tabulated list of adverse reactions

The safety of sugammadex has been evaluated in 3,519 unique subjects across a pooled phase I-III safety database. The following adverse reactions were reported in placebo controlled trials where subjects received anaesthesia and/or neuromuscular blocking agents (1,078 subject exposures to sugammadex versus 544 to placebo):

[Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000)]

System organ class	Frequencies	Adverse reactions (Preferred terms)
Immune system disorders	Uncommon	Drug hypersensitivity reactions (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Cough

Injury, poisoning and procedural complications	Common	Airway complication of anaesthesia Anaesthetic complication (see section 4.4) Procedural hypotension Procedural complication

Description of selected adverse reactions 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.
In postmarketing reports, hypersensitivity has been observed for sugammadex as well as for sugammadex-rocuronium complex.

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 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%).
In the Pooled Phase 1 database, AEs considered common (≥ 1/100 to < 1/10) or very common (≥ 1/10) and more 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%).

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

In studies of paediatric 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 adverse reaction 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.

Reporting of suspected adverse reactions:
Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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 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

Pharmacotherapeutic group: all other therapeutic products, antidotes, 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 (4 mg/kg)	Neostigmine (70 mcg/kg)
Rocuronium N Median (minutes) Range	 37 2.7 1.2-16.1	 37 49.0 13.3-145.7
Vecuronium N Median (minutes) Range	 47 3.3 1.4-68.4	 36 49.9 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, 2 mg/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 (2 mg/kg)	Neostigmine (50 mcg/kg)
Rocuronium N Median (minutes) Range	 48 1.4 0.9-5.4	 48 17.6 3.7-106.9
Vecuronium N Median (minutes) Range	 48 2.1 1.2-64.2	 45 18.9 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 2 mg/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 (2 mg/kg)	Cis-atracurium and neostigmine (50 mcg/kg)
N Median (minutes) Range	34 1.9 0.7-6.4	39 7.2 4.2-28.2

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 rocuroniuminduced 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 (16 mg/kg)	Succinylcholine (1 mg/kg)
N Median (minutes) Range	55 4.2 3.5-7.7	55 7.1 3.7-10.5

In a pooled analysis the following recovery times 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

Renal impairment:
Two open label studies compared the efficacy and safety of sugammadex in surgical patients with and without severe renal impairment. In one study, sugammadex was administered following rocuronium induced blockade at 1-2 PTCs (4 mg/kg; N=68); in the other study, sugammadex was administered at reappearance of T_2 (2 mg/kg; N=30). Recovery from blockade was modestly longer for patients with severe renal impairment relative to patients without renal impairment. No residual neuromuscular blockade or recurrence of neuromuscular blockade was reported for patients with severe renal impairment in these studies.

Morbidly obese patients:
A trial of 188 patients who were diagnosed as morbidly obese 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).

Paediatric Population:
A trial of 288 patients aged 2 to < 17 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.

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 adverse reaction 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.

5.2 Pharmacokinetic properties

The sugammadex pharmacokinetic parameters were calculated from the total sum of noncomplex- bound and complex-bound concentrations of sugammadex. Pharmacokinetic parameters as clearance and volume of distribution are assumed to be the same for non-complexbound 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 anaesthetised patients with normal renal function the elimination half-life (t1/2) 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 t1/2 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.

Table 8: A summary of sugammadex pharmacokinetic parameters stratified by age and renal function is presented below:

Selected patient characteristics				**Mean Predicted PK parameters (CV*%)**		
Demographics Age Body weight	Renal function Creatinine clearance (ml/min)			Clearance (ml/min)	Volume of distribution at steady state (L)	Elimination half-life (hr)
Adult	Normal		100	84 (24)	13	2 (22)

40 years 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 years 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 years 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 years 29 kg	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 years 16 kg	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

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.

Bodyw eight:

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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity potential, and toxicity to reproduction, local tolerance or compatibility with blood.

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 0.3 % (to adjust pH)
Sodium hydroxide 0.04 % (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

3 years

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

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

Glass vial with chlorobutyl rubber stopper with aluminium seal and plastic flip-off cap. Pack sizes:
1 vial of 2 ml
10 vials of 2 ml
1 vial of 5 ml
10 vials of 5 ml

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

[Invented 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%).

The infusion line should be adequately flushed (e.g., with 0.9% sodium chloride) between administration of [Invented name] and other medicinal products.

Use in the paediatric population

For paediatric patients [Invented name] 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. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

CTD13002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15TH JANUARY,2026

10. DATE OF REVISION OF THE TEXT

15TH JANUARY,2026