SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUGRINO 500 mg/5 mL Solution for IV Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 5 mL contains:

Active substance:

Sugammadex sodium ..... 544 mg (equivalent to 200 mg sugammadex)

Excipients with known effect:

Sodium hydroxide ..... q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Vial containing a homogeneous, clear, and colorless to slightly yellow solution, free of visible foreign matter. 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.

For pediatric population: Sugammadex is only recommended for reversal of rocuronium-induced neuromuscular blockade in children and adolescents aged 2 years and over.

4.2 Posology and method of administration

Posology / frequency and duration of administration

Sugammadex should only be administered by, or under the supervision of an anesthetist. 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 anesthetic 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 neuromuscular recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 3 minutes (see section 5.1).

A dose of 2 mg/kg sugammadex is advised, if spontaneous recovery from neuromuscular blockade 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.

Method of administration

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

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.

Hepatic impairment

Since sugammadex is largely excreted via the kidneys, there is no need for dose adjustment in patients with mild to moderate hepatic impairment. Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of sugammadex in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see section 4.4).

Pediatric population

Children and adolescents (2-17 years):

SUGRINO 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-induced neuromuscular 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 T_2 (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 sugammadex use 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 advised until further data become available.

Elderly patients
After giving 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 from neuromuscular blockade in elderly tend to be slower, the same dose advice as for adults should be followed (see section 4.4).

Obese patients
In obese patients, including morbidly obese patients (body mass index $\geq$ 40 kg/m^2), the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults can be followed.

4.3 Contraindications
Contraindicated in patients with hypersensitivity to the active substance or any of the other ingredients of this medicinal product (see section 6.1).

4.4 Special warnings and precautions for use
As with normal post-anesthetic 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.
In case of recurrence of neuromuscular blockade 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 labeled 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 (see section 4.4). 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 sections 4.2 and 4.8).

Effect on hemostasis:
In a study in subjects, 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 the 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 database (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 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 anesthesiologist needs to decide if the benefits outweigh the possible risk of bleeding complications, taking into consideration the patient's history of bleeding episodes and type of surgery scheduled. If sugammadex is administered to these patients, monitoring of hemostasis 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 readministration of rocuronium 1.2 mg/kg within 30 minutes after sugammadex administration.

Based on PK modeling, 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 anesthesia:
When neuromuscular blockade was reversed intentionally in the middle of anesthesia in clinical trials, signs of light anesthesia were noted occasionally (movement, coughing, grimacing, and suckling of the tracheal tube).
If neuromuscular blockade is reversed while anesthesia is continued, additional doses of anesthetic 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 (see section 4.8). Bradycardia may occasionally lead to cardiac arrest. 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:
Sugammadex has not been studied in patients taking rocuronium or vecuronium in the ICU setting.

Use for reversal of neuromuscular blocking agents other than Rocuronium/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 the 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).

Sodium:
This medicinal product contains less than 1 mmol sodium (23 mg) per mL, i.e., it is essentially “sodium-free”. If 2.5 mL or more of solution must be administered, consideration should be given to whether the patient is on a controlled sodium diet.

4.5 Interactions 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 the 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 that caused displacement should be stopped in case of an infusion. In situations where 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 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 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 on the same day as an oral contraceptive is taken, reference is made to missed dose advice in the package leaflet of the oral contraceptive for any measures to be taken.

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 recommendations in the package leaflet.

Interactions due to the lasting effect of rocuronium or vecuronium:

When medicines that potentiate neuromuscular blockade are used in the post-operative period, special attention should be paid to possibility of recurrence of neuromuscular blockade. Please refer to the package leaflet of rocuronium or vecuronium for a list of the specific medicinal products that 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 micrograms/ml (peak plasma level following 8 mg/kg bolus injection).

In a study in subjects, 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).

Additional information on special populations:

Pediatric patients:

No formal interaction studies have been performed. The above mentioned interactions for adults and the warnings in section 4.4 should also be considered for the pediatric population.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category “B”.

Women of childbearing potential/Birth control (contraception):

Sugammadex interacts with oral contraceptive drugs. Therefore, an alternative, effective and reliable birth control method should be used during the treatment.

If sugammadex is given on the same day as an oral contraceptive is taken, reference is made to missed dose advice in the package leaflet of the oral contraceptive for any measures to be taken.

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

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/fetal development, parturition, or postnatal development.

Caution should be exercised when administering sugammadex to pregnant women.

Breastfeeding

It is unknown if sugammadex is excreted in human milk. Animal studies have shown excretion of sugammadex in 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, considering the benefit of breast-feeding for the child and the benefit of the therapy for the mother.

Fertility

The effects of 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

SUGRINO is administered concomitantly with neuromuscular blocking agents and anesthetics 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 anesthesia, anesthetic complications, procedural hypotension, and procedural complications (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 anesthesia and/or neuromuscular blocking agents (1,078 subject exposures to sugammadex versus 544 to placebo):

Undesirable effects are listed in the categories below: 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, unknown: cannot be estimated from the available data.

System organ class	Frequency	Adverse reactions
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 complications of anesthesia Anesthetic complication (see section 4.4) Procedural hypotension Procedural complications

Descriptions of the selected adverse reactions:

Drug hypersensitivity reactions:

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

These varied in severity 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 may include flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of the tongue, swelling of pharynx, bronchospasm, and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal.

Airway complications of anesthesia:

Airway complications of anesthesia included resistance against the endotracheal tube, coughing, mild resistance, arousal reaction during surgery, coughing during the anesthetic procedure or during surgery, or anesthetic procedure-related spontaneous breath of the patient.

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).

Procedural complications:

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

Marked bradycardia:

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

Recurrence of neuromuscular blockade:

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose adjusted 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 subjects:

A randomized, double-blind study examined the incidence of drug hypersensitivity reactions in healthy subjects 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%).

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%).

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 patients: 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 with patients who were assessed as American Society of Anesthesiologists (ASA) Class 3 or 4 (patients with severe systemic disease or 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
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and treatment
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 well tolerated at doses up to 96 mg/kg. No dose-related adverse events nor serious adverse events were reported.
Sugammadex can be removed from the body using hemodialysis 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, 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 randomized 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 micrograms /kg)
Rocuronium		
N	37	37
Median (minutes)	2.7	49
Range	1.2-16.1	13.3-145.7
Vecuronium		
N	47	36
Median (minutes)	3.3	49.9
Range	1.4-68.4	46-312.7

Routine Reversal Moderate Neuromuscular Block:
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 randomized 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 micrograms /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 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 micrograms/kg)
N	34	39
Median (minutes)	1.9	7.2
Range	0.7-6.4	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 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 (16 mg/kg)	Succinylcholine (1 mg/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 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

	0.9 T_4/T_1	0.8 T_4/T_1	0.7 T_4/T_1
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 (body mass index $\geq$ 40 kg/m^2) 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. In pooled data by depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio of $\geq$ 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).

Pediatric patients:
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 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 micrograms/kg up to 5 mg maximum dose) + glycopyrrolate (10 micrograms/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
General properties:
Absorption:
The sugammadex pharmacokinetic parameters were calculated from the total sum of non-complex-bound and complex-bound concentrations of sugammadex. Pharmacokinetic parameters such as clearance and volume of distribution are assumed to be the same for non-complex-bound and complex-bound sugammadex in anesthetized subjects.

Distribution
Observed steady-state volume of distribution of sugammadex is approximately 11 to 14 liters 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.

Biotransformation:
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 anesthetized patients with normal renal function, the elimination half-life 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 feces or expired air was less than 0.02% of the dose. Sugammadex administration to healthy subjects caused high renal elimination of rocuronium in complex.

Linearity/Non-linearity:
Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose.

Patient characteristics:

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 impairment.

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 to severe renal impairment, respectively. Sugammadex concentration was no longer detectable beyond 7 days post-dose in subjects with severe renal impairment.

Table 8: The predicted pharmacokinetic parameters of sugammadex based on compartmental modeling (three-compartments) are shown below by age group and renal function:

Selected Patient Characteristics			**Predicted PK parameters (CV*)**		
Demographic characteristics Age Body weight	Renal function (creatinine clearance, mL/min)		Clearance, (mL/min)	Volume of distribution at steady state, liters (L)	Elimination half-life (hours)
Adult 40 years 75 kg	Normal	100	84 (24%)	13	2 (22%)
	Impaired	Mild 50	47 (25%)	14	4 (22%)
		Moderate 30	28 (24%)	14	7 (23%)
		Severe 10	8 (25%)	15	24 (25%)
Elderly 75 years 75 kg	Normal	80	70 (24%)	13	3 (21%)
	Impaired	Mild 50	46 (25%)	14	4 (23%)
		Moderate 30	28 (25%)	14	7 (23%)
		Severe 10	8 (25%)	15	24 (24%)
Adolescent 15 years 56 kg	Normal	95	72 (25%)	10	2 (21%)
	Impaired	Mild 48	40 (24%)	11	4 (23%)
		Moderate 29	24 (24%)	11	6 (24%)
		Severe 10	7 (25%)	11	22 (25%)
Middle childhood 9 years 29 kg	Normal	60	40 (24%)	5	2 (22%)
	Impaired	Mild 30	21 (24%)	6	4 (22%)
		Moderate 18	12 (25%)	6	7 (24%)
		Severe 6	3 (26%)	6	25 (25%)
Early childhood 4 years 16 kg	Normal	39	24 (25%)	3	2 (22%)
	Impaired	Mild 19	11 (25%)	3	4 (23%)
		Moderate 12	6 (25%)	3	7 (24%)
		Severe 4	2 (25%)	3	28 (26%)

*CV=Coefficient of Variation

Gender:

No gender-related 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 were 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 its residual was observed in the bones and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex does not adversely affect tooth color or bone quality, bone structure, or bone metabolism. Sugammadex has no effects on fracture repair and remodeling of bone.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

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
24 months.

After first opening and dilution of the vial, chemical and physical in-use stability have been demonstrated for 48 hours at 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 would normally not be longer than 24 hours at 2°C to 8°C. The product diluted with 0.9% NaCl solution, 5% glucose solution, 0.45% NaCl + 2.5% glucose solution, ringer's lactate solution, ringer's solution, 0.9% NaCl + 5% glucose solution should be used within 48 hours if stored at room temperature at 25°C, within 24 hours if stored between 2°C - 8°C.

6.4 Special precautions for storage
Store at room temperature below 25°C.

For storage conditions of the diluted product, see section 6.3.

6.5 Nature and contents of container
The primary packaging materials of this product are a 6 CC Type I colorless transparent glass vial, gray-colored fluoropolymer-coated bromobutyl rubber stopper, and an aluminum flip-off with a white polypropylene cap. The product is provided in a cardboard box including 10 vials that are separated by a separator, and is delivered with a package leaflet.

6.6 Special precautions for disposal and other handling
SUGRINO can be injected into the intravenous line of a running infusion with the following intravenous solutions: The product is diluted with reconstitution solutions (0.9% NaCl solution, 5% glucose solution, 0.45% NaCl + 2.5% glucose solution, Ringer's lactate solution, Ringer's solution, 0.9% NaCl + 5% glucose solution) to a concentration of 10 mg/mL

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

Use in pediatric population: For pediatric patients, SUGRINO can be diluted using sodium chloride 9 mg/ml (0.9%) to a concentration of 10 mg/ml.

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

7. MA HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MA NUMBER
2023/2

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of first authorization : 13.01.2023
Date of renewal of authorization :

10. DATE OF REVISION OF THE TEXT