SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUGAVER 200 mg/2 mL I.V. solution for injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:
2 mL of SUGAVER
contains 250 mg of sugammadex sodium equivalent to 200 mg of sugammadex.

Excipients:
Sodium hydroxide 9.7 mg (per 1 mL)

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Injectable solution
Amber ampoule with a clear and colorless or slightly yellow solution.
The pH is between 7-8 and the osmolality is between 300-500 mOsm/kg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Reversal of neuromuscular block caused by rocuronium or vecuronium.
For pediatric population: It is recommended that sugammadex be used only in reversal of rocuronium-induced neuromuscular block 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 used by or under the supervision of an anesthesiologist. It is recommended to use an appropriate neuromuscular monitoring technique to monitor recovery of neuromuscular block. (see Section 4.4).

The recommended dose of sugammadex depends on the level of neuromuscular block to be reversed.

The recommended dose is not dependent on the anesthetic regimen.

Sugammadex can be used to reverse varying degrees of neuromuscular block caused by rocuronium or vecuronium.

Adults:
Routine Reversal:
A dose of 4.0 mg/kg sugammadex is recommended if reversal of neuromuscular block has reached at least 1–2 post-tetanic counts (PTC) following rocuronium or vecuronium-induced block. The median time to recovery of a T4/T1 ratio of 0.9 is around 3 minutes (see Section 5.1)

If spontaneous reversal of neuromuscular block has occurred with reappearance of T2 following rocuronium- or vecuronium-induced block, a dose of 2 mg/kg sugammadex is recommended. The median time to recovery of the T4/T1 ratio of 0.9 is around 2 minutes (see Section 5.1)

Use of recommended doses for routine reversal will result in a slightly faster median time to recovery of rocuronium's T4/T1 ratio of 0.9 compared with vecuronium-induced neuromuscular block (see Section 5.1)

Immediate reversal of rocuronium-induced block:
Following rocuronium administration, a dose of 16 mg/kg sugammadex is recommended if clinically needed for immediate reversal.

When a 16 mg/kg sugammadex dose is administered 3 minutes after a bolus dose of 1.2 mg/kg rocuronium bromide, the median time to recovery of a T4/T1 ratio of 0.9 can be expected to be approximately 1.5 minutes (see Section 5.1)

There are no data to recommend the use of sugammadex for rapid reversal following vecuronium-induced block.

Re-administration of sugammadex:
In the exceptional case where neuromuscular block reoccurs after surgery (see Section 4.4). After an initial dose of 2 mg/kg or 4 mg/kg, it is recommended to give 4 mg/kg sugammadex again. After a second dose of sugammadex, the patient should be closely monitored to ensure that neuromuscular function has returned.

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

Route of administration:
Sugammadex should be administered intravenously as a single bolus injection. Bolus injection should be given rapidly within 10 seconds directly into a venous vein or into an existing I.V. route. (see Section 6.6). Sugammadex has only been administered as a single bolus injection in clinical trials.

Additional information on special populations:

Renal Impairment:

Not recommended for patients with severe renal impairment (including patients requiring dialysis with creatinine clearance <30 mL/min) (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.

In patients with mild to moderate renal impairment (creatinine clearance ≥30 to <80 mL/min), the same dose recommendations can be followed as in adults without renal impairment.

Hepatic impairment:

Since sugammadex is largely excreted by the kidneys, no dose adjustment is required 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:

Limited data are available for the pediatric population (only one study of T2 reappearance following rocuronium-induced block).

Children and Adolescents:

In children and adolescents (2–17 years of age), 2 mg/kg of sugammadex is recommended for routine reversal of rocuronium-induced block in case of recurrence of T2.

SUGAVER can be diluted from 100 mg/mL to 10 mg/mL to improve dosage accuracy in the pediatric population (see section 6.6).

Other routine reversal situations have not been explored and are therefore not recommended until further data are available.

Rapid reversal has not been studied in children and adolescents and is therefore not recommended until further data are available.

Newborns (full-term born) and infants:

There is only limited experience with the use of sugammadex in infants (30 days to 2 years of age) and no studies have been conducted in neonates (less than 30 days old). Therefore, the use of sugammadex in neonates and infants is not recommended until further data are available.

Geriatric population:

If T2 reappears following rocuronium-induced block, the median time to recovery of a T4/T1 ratio of 0.9 after sugammadex administration is 2.2 minutes in adults (18–64 years) versus 2.2 minutes in the elderly (65–74 years) 2 .6 minutes and 3.6 minutes in the very elderly (75 years

and older). The same dose recommendation should be followed for the elderly as for adults, although recovery times in neuromuscular block in the elderly tend to be slower (see section 4.4).

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

4.3. Contraindications

It is contraindicated in patients with hypersensitivity to the active substance or any of its ingredients (see section 6.1).

4.4. Special warnings and precautions for use

As with normal post-anesthetic practice following neuromuscular block, it is recommended that the patient be followed up for adverse events, including re-occurrence of neuromuscular block, in the immediate post-operative period.

Monitoring of respiratory function during reversal of neuromuscular block:
Following reversal of neuromuscular block, ventilatory support is mandatory for patients until adequate spontaneous breathing is achieved. Even if recovery from neuromuscular block is complete, ventilatory support may still be necessary because other drugs used before and after the operation may suppress respiratory function.

If neuromuscular block reoccurs following extubation, adequate ventilation should be provided.

Reoccurrence of neuromuscular block:
In clinical studies where sugammadex was administered using a dose adjusted for the depth of neuromuscular blockade and patients were treated with rocuronium or vecuronium, the incidence of recurrence of neuromuscular blockade was 0.20% based on neuromuscular monitoring or clinical evidence (see section 4.4). Use of lower than recommended doses may increase the risk of recurrence of neuromuscular block and is not recommended (see sections 4.2 and 4.8).

Effect on hemostasis:
In a study in volunteers, 4 mg/kg and 16 mg/kg sugammadex caused 17% and 22% maximal prolongations in aPTT (activated partial thromboplastin time) and 11% and 22% in PT (INR), respectively. These limited mean aPTT and prothrombin time international normalized ratio [PT(INR)] prolongations were determined to be of short duration (≤30 minutes). Based on a clinical database (n=3519) and a specific study conducted in 1184 patients undergoing hip fracture/major joint replacement surgery, sugammadex alone (4 mg/kg) or in combination with anticoagulants has a clinical effect on the incidence of peri- or post-operative bleeding

complications. showed no noticeable effect.

A pharmacodynamic interaction (aPTT and PT prolongation) has been noted with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran in *in vitro* experiments. This pharmacodynamic interaction is not clinically relevant in patients receiving routine postoperative prophylactic anticoagulation. Caution should be exercised when considering the use of sugammadex in patients receiving therapeutic anticoagulation for a pre-existing or comorbid condition.

An increased risk of bleeding cannot be excluded in the following patients:
- Hereditary vitamin K-dependent coagulation factor deficiencies
- Patients with pre-existing coagulopathies
- Those who take coumarin derivatives and have an INR higher than 3.5
- Patients using anticoagulants and taking 16 mg/kg sugammadex

If there is a medical need to administer sugammadex to these patients, the anesthesiologist must decide whether the benefits outweigh the potential risks of bleeding complications, taking into account the patient's history of bleeding episodes and the type of surgery planned. If sugammadex is administered to these patients, monitoring of hemostasis and coagulation parameters is recommended.

Holding Time for Re-administration of Neuromuscular Blocking Agents After Sugammadex Reversal:
Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg of sugammadex):
Table 1:

Minimum Holding time	**NMBA and the dose to be administered**
5 minutes	1.2 mg/kg rocuronium
4 hours	0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium

With re-administration of 1.2 mg/kg rocuronium up to 30 minutes after sugammadex administration, the onset of neuromuscular block may be prolonged up to about 4 minutes and the duration of neuromuscular block shortened to about 15 minutes.

Based on pharmacokinetic modeling, the recommended holding time for reuse of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after routine reversal with sugammadex in patients with mild or moderate renal impairment should be 24 hours. If a shorter holding period is required, the rocuronium dose for new neuromuscular block should be 1.2 mg/kg.

Re-administration of rocuronium or vecuronium after emergency reversal (16 mg/kg sugammadex):
In the very rare cases where this may be necessary, a holding period of 24 hours is recommended. If neuromuscular block is necessary before the recommended holding period has elapsed, a non-steroidal neuromuscular blocking agent should be used. The onset of action of a depolarizing neuromuscular blocking agent may be slower than expected because a significant number of postjunctional nicotine receptors may still be bound to the neuromuscular blocking agent.

Renal Impairment:
The use of sugammadex is not recommended in patients with severe renal impairment, including those requiring dialysis (see section 5.1).

Alleviation of the effect of anesthesia:
In clinical studies, when neuromuscular block was reversed in mid-anaesthesia, signs of easing of anesthesia were noted (movement, coughing, grimacing, and retraction of the tracheal tube).

If neuromuscular block is reversed while anesthesia is maintained, additional doses of anesthetic and/or opioids should be given as clinically indicated.

Significant bradycardia:
In rare cases, significant bradycardia has been observed within minutes after administration of sugammadex to reverse neuromuscular block (see section 4.8). Bradycardia can sometimes cause cardiac arrest. During and after reversal of neuromuscular block, patients should be closely monitored for haemodynamic changes. If clinically significant bradycardia is observed, treatment with anticholinergic agents such as atropine should be instituted.

Hepatic Impairment:
Since sugammadex is not metabolized or excreted in the liver, specific studies have not been conducted in patients with hepatic impairment. It should be used with great caution in patients with severe hepatic impairment. See information on effect on hemostasis when hepatic impairment is accompanied by coagulopathy.

Use in the intensive care unit:
The use of sugammadex has not been studied in patients receiving rocuronium or vecuronium in the intensive care unit setting.

Use for reversal of neuromuscular blocking agents other than rocuronium/vecuronium:
Sugammadex should not be used to reverse block caused by non-steroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.

Sugammadex should not be used to reverse neuromuscular block caused by steroidal neuromuscular blocking agents other than rocuronium or vecuronium, due to the lack of efficacy and safety data for such conditions. Although there are limited data on reversal of pancuronium-induced block, the use of sugammadex in this situation is not recommended.

Delayed reversal:
Conditions associated with prolonged circulation time such as cardiovascular disease, old age (see Section 4.2 for recovery time in the elderly), or edema status (eg, severe hepatic impairment) may result in longer recovery times in neuromuscular block.

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

Patients on a sodium diet:
Each mL of solution contains 9.7 mg of sodium. Contains less than 23 mg of sodium; so it's actually "sodium free". If a solution of 2.4 mL or more needs to be administered, it should be considered whether the patient is on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

The information presented in this section is based on simulations using a model that considers the binding affinity between sugammadex and other drugs, non-clinical trials, clinical studies, and the pharmacodynamic effects of neuromuscular blocking agents, and the pharmacokinetic interaction between neuromuscular blocking agents and sugammadex. Based on these data, clinically significant pharmacodynamic interactions with other drugs are not expected, except for the following.
Substitution interactions cannot be excluded for toremifene and fusidic acid (clinically significant capture interactions are not expected).

For hormonal contraceptives, a clinically significant capture interaction cannot be excluded (displacement interactions are not expected).

Interactions Potentially Affecting the Efficacy of Sugammadex (Substitution interactions):
Due to the administration of certain drugs after sugammadex, rocuronium or vecuronium can theoretically be replaced by sugammadex. As a result, reoccurrence of neuromuscular block can be observed. In this case, the patient should be ventilated. In the case of infusion, administration of the drug that causes substitution should be stopped. Where potential substitution interactions can be expected, patients; Following the parenteral administration of another medicinal product in the 7.5 hour period following sugammadex administration, it should be carefully monitored (for a maximum of about 15 minutes) for signs of reoccurrence of neuromuscular block.

Toremifene:
For toremifene, which has a relatively high affinity constant and plasma concentrations compared to sugammadex, substitution of vecuronium or rocuronium from the complex with sugammadex may occur. Therefore, clinicians should be aware that the recovery of the T4/T1 ratio with 0.9 may be delayed in patients receiving toremifene on the day of the operation.

Intravenous administration of fusidic acid:
The use of fusidic acid in the preoperative period may cause some delay in the recovery of the T4/T1 ratio up to 0.9. Recurrence of neuromuscular block is not expected in the post-operative period because fusidic acid is given by infusion over several hours and blood levels rise in 2-3 days. For re-administration of sugammadex, see section 4.2.

Interactions Potentially Affecting the Effectiveness of Other Drugs (capture interactions):
Due to the administration of sugammadex, certain drugs may become less effective due to reduced (free) plasma concentrations. If such is observed, the clinician is advised to re-administer the medicinal product as appropriate, administer a therapeutically equivalent medicinal product preferably from a different chemical class, and/or consider non-pharmacological interventions.

Hormonal Contraceptives:
The interaction between 4 mg/kg sugammadex and a progestogen can result in a reduction in progestogen exposure (34% AUC) similar to taking a daily dose of an oral contraceptive 12 hours late (taking 12 hours late may lead to reduced efficacy). The effect is expected to be less for estrogens. Therefore, administration of a bolus dose of sugammadex is considered to be equivalent to a missed daily dose of oral contraceptive steroids (alone or combined progestogen). If an oral contraceptive is required on the day of administration of sugammadex, refer to the skipped dose recommendation in the oral contraceptive leaflet for any precautions to be taken.

If non-oral hormonal contraceptives are used, the patient should use an additional non-hormonal method of contraception for the next 7 days.

Interactions resulting from the continued effect of rocuronium or vecuronium:
When drugs that increase neuromuscular block are used in the post-operative period, particular attention should be paid to the possibility of reoccurrence of neuromuscular block. See the leaflet for rocuronium or vecuronium for a list of specific drugs that increase neuromuscular block. If reoccurrence of neuromuscular block is observed, the patient may need to be ventilated and sugammmedex to be re-administered (see section 4.2).

Interactions with Laboratory Tests:
In general, sugammadex does not interfere with laboratory tests, with the possible exception of serum progesterone determination. Interference was observed with this assay at plasma

sugammadex concentrations of 100 microgram/mL (peak plasma level after 8 mg/kg bolus injection).

In a study in volunteers, 4 mg/kg and 16 mg/kg sugammadex caused 17% and 22% maximum mean prolongations in aPTT and 11% and 22% in PT (INR), respectively. These limited mean aPTT and PT(INR) prolongations were determined to be of short duration (≤30 minutes).

A pharmacodynamic interaction (aPTT and PT prolongation) has been noted with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran in *in vitro* experiments (see section 4.4).

Additional information on special populations:
Pediatric population:
No formal interaction studies have been conducted. 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 advice:
Pregnancy category: B

Women of childbearing potential / contraception:
Sugammadex interacts with oral contraceptives. Therefore, an alternative, effective and reliable method of contraception should be used during the treatment.

If an oral contraceptive is required on the day of administration of sugammadex, refer to the skipped dose recommendation in the oral contraceptive leaflet for any precautions to be taken.

If non-oral hormonal contraceptives are used, the patient should use an additional non-hormonal method of contraception for the next 7 days.

Pregnancy period
No clinical data on exposed pregnancies are available for sugammadex.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Care should be taken when administering sugammadex to pregnant women.

Lactation period
It is not known whether sugammadex passes into breast milk. Animal studies have shown that sugammadex is excreted in breast milk. Oral absorption of cyclodextrins is generally low and no effect on the suckling child is expected at a dose given to the nursing mother. A decision should

be made whether to discontinue breastfeeding or to discontinue sugammadex therapy, taking into account the benefit of breast milk for the infant and the benefit of therapy for the mother.

Reproductive ability / Fertility
The effects of sugammadex on human fertility have not been studied. Animal studies examining fertility have not revealed harmful effects.

4.7. Effects on ability to drive and use machines
SUGAVER has no known effects on the ability to drive and use machines.

4.8. Undesirable effects
Summary of the safety profile
SUGAVER is used concurrently with neuromuscular blocking agents and anesthetics in surgical patients. It is therefore difficult to assess the cause of adverse effects.
The most commonly reported adverse reactions in surgical patients were cough, airway complication of anesthesia, anesthetic complications optional hypotension, and optional complication (common (≥1/100 to <1/10)).

Table 2: Tabulated list of adverse reactions
The safety of sugammadex was evaluated in 3,519 individual patients in a combined Phase I-III safety database. The following adverse reactions have been reported in placebo-controlled studies in which patients received anesthetics and/or neuromuscular blocking agents (1,078 patients received sugammadex and 544 patients received placebo):

Undesirable effects are listed in the following categories: Very common (≥1/10); common (≥1/100 to < 1 /10); uncommon (≥1/1000 and <1/100); rare (≥1/10.000 and <1/1000); very rare (< 1/10.000); unknown (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Immune system diseases	Uncommon	Drug-induced hypersensitivity reactions (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Cough
Injury, poisoning and procedural complications	Common	Respiratory complication of anesthesia Anesthetic complication (see Section 4.4) Procedural hypotension Complications related to the procedure performed

Description of selected adverse reactions

Drug-induced hypersensitivity reactions: Some patients and volunteers developed hypersensitivity reactions, including anaphylaxis (for information on volunteers, please see the Information on Healthy Volunteers section below). These reactions were uncommonly reported in clinical trials in surgical patients; post-marketing frequency reports are unknown.

These reactions ranged from isolated skin reactions to severe systemic reactions (eg, anaphylaxis, anaphylactic shock) and have been reported in patients who had never been exposed to sugammadex.

Hot flashes, urticaria, erythematous skin rashes, (severe) hypotension, tachycardia and swelling of the tongue and pharynx, bronchospasm and pulmonary obstructive events are the accompanying symptoms. Severe allergic reactions can result in death.

Respiratory Complication of Anesthesia:

Respiratory complications of anesthesia included involuntary resistance to the endotracheal tube, coughing, mild resistance, awake reaction during surgery, coughing during the anesthesia procedure or surgery, or spontaneous breathing of the patient due to the anesthesia procedure.

Anesthetic Complication:

Anesthetic complications indicative of restoration of neuromuscular function are movement of the body or limbs during anesthetic procedures or surgery, or coughing, grimacing, or backward shift of the endotracheal tube (see Section 4.4).

Complications related to the procedure:

Procedural complications include cough, tachycardia, bradycardia, movement, and increased heart rate.

Significant bradycardia:

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

Reoccurrence of neuromuscular block:

In clinical studies (N=2.022) where sugammadex was administered using a dose adjusted for the depth of neuromuscular block and patients were treated with rocuronium or vecuronium, the incidence of recurrence of neuromuscular block was 0.20% based on neuromuscular monitoring or clinical evidence (see section 4.4).

Information on Healthy Volunteers

A randomized, double-blind study examined the incidence of drug-induced 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. No reports of anaphylaxis were received after placebo or sugammadex 4 mg/kg. There was only one reported case of adjudicated anaphylaxis after the first dose of sugammadex 16 mg/kg (incidence 0.7%). There was no evidence of an increase in the frequency or severity of hypersensitivity with repeated dosing of sugammadex.

In a previous study of similar design, three cases of adjudicated anaphylaxis were reported (incidence 2.0%), all after sugammadex 16 mg/kg.

Adverse events evaluated as common (≥1/100 to <1/10) or very common (≥1/10) in sugammadex-treated patients in the unified Phase 1 database and reported more frequently than in the placebo group, taste disturbance (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:
Bronchospasm was reported as an adverse event possibly related to sugammadex in a clinical study and post-marketing data in patients with known prior pulmonary complications. As with all patients with pulmonary complications, the doctor should be aware of the possibility of developing bronchospasm.

Pediatric population:
Limited database, the safety profile of sugammadex (up to 4 mg/kg) in pediatric patients appears to be similar to that in adults.

Morbidly obese patients:
In a specific clinical study in morbidly obese patients, the adverse reaction profile was generally similar to that observed in adult patients in the pooled Phase 1 to 3 studies (see Table 2).

Patients with severe systemic disease:
In a study of patients rated as American Society of Anesthesiologists (ASA) Class 3 or 4 (patients with severe systemic disease or patients with severe life-threatening systemic disease), the adverse reaction profile in these ASA Class 3 and 4 patients was generally pooled Phase 1 was similar to that of adult patients in studies through 3 (see Table 2) (see Section 5.1).

Reporting of suspected adverse reactions
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. Health professionals should report any suspected adverse reactions to the relevant health authority. (www.titck.gov.tr; e-mail:tufam@titck.gov.tr; tel: 0 800 314 00 08; faks: 0 312 218 35 99).

4.9. Overdose and treatment

In clinical studies, 1 case of accidental overdose with 40 mg/kg was reported without any significant undesirable effects. In the human tolerance study, sugammadex was well tolerated at doses up to 96 mg/kg. No dose-related adverse events or serious adverse events were reported.

Sugammadex can be removed from the body using hemodialysis with a high flow filter (which cannot be done with a low flow filter). Based on clinical studies, sugammadex concentrations in plasma decrease by approximately 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 that is a selective muscle relaxant binding agent. Neuromuscular blocking agents form a complex with rocuronium or vecuronium in plasma and reduce the amount of neuromuscular blocking agent available to bind to nicotinic receptors at the neuromuscular junction. This results in reversal of rocuronium or vecuronium-induced neuromuscular blockade.

Pharmacodynamic effects:

Sugammadex is a combination of rocuronium-induced block (0.6, 0.9, 1.0, and 1.2 mg/kg rocuronium bromide with and without maintenance doses) and vecuronium-induced block (with and without maintenance doses) of varying time and depth. 0.1 mg/kg vecuronium bromide) was administered at doses ranging from 0.5 mg/kg to 16 mg/kg in dose-response studies. A significant dose-response relationship was observed in these studies.

Clinical efficacy and safety

Sugammadex can be administered at various time points after rocuronium or vecuronium bromide administration:

Routine Reversal – Deep Neuromuscular Block:

In a pivotal study, patients were randomized to either rocuronium or vecuronium. After the last dose of rocuronium or vecuronium, 4.0 mg/kg sugammadex or 70 microgram/kg neostigmine was administered randomly at 1-2 PTCs. The time from the start of sugammadex or neostigmine administration to recovery of a T4/T1 ratio of 0.9 is as follows:

Table 3: *Time to Recovery of T4/T1 Ratio of 0.9 from Sugammadex or Neostigmine Administration in Case of Deep Neuromuscular Block (1–2 PTC) After Rocuronium or Vecuronium Administration (minutes)*

Neuromuscular Block Agent	Treatment Regimen	
	Sugammadex (4.0 mg/kg)	Neostigmine (70 micrograms/kg)
Rocuronium		
N	37	37
Median (minutes)	2.7	49.0
Interval	1.2–16.1	13.3–145.7
Vecuronium		
N	47	36
Median (minutes)	3.3	49.9
Interval	1.4–68.4	46.0–312.7

Routine Reversal Moderate Neuromuscular Block:
In another pivotal study, patients were randomized to rocuronium or vecuronium. In case of recurrence of T2 after the last dose of rocuronium or vecuronium, 2.0 mg/kg sugammadex or 50 microgram/kg neostigmine was administered randomly. The time from the start of sugammadex or neostigmine administration to recovery of a T4/T1 ratio of 0.9 is as follows:

Table 4: *If T2 Reappears After Rocuronium or Vecuronium Administration, Time from Sugammadex or Neostigmine Administration to Recovery of a T4/T1 Ratio of 0.9 (minutes)*

Neuromuscular Block Agent	Treatment Regimen	
	Sugammadex (2.0 mg/kg)	Neostigmine (50 micrograms / kg)
Rocuronium		
N	48	48
Median (minutes)	1.4	17.6
Interval	0.9–5.4	3.7–106.9
Vecuronium		
N	48	45
Median (minutes)	2.1	18.9
Interval	1.2–64.2	2.9–76.2

Reversal of rocuronium-induced neuromuscular block with sugammadex was compared with reversal of cistracurium-induced neuromuscular block with neostigmine. In case of recurrence of T2, a dose of 2.0 mg/kg sugammadex or 50 microgram/kg neostigmine was administered. Sugammadex provided faster reversal of rocuronium-induced neuromuscular block compared to reversal of cis-atracurium-induced neuromuscular block with neostigmine.

Table 5: *If T2 Reappears After Rocuronium or Cis-Atracurium Administration, Time From Sugammadex or Neostigmine Administration to Recovery of a T4/T1 Ratio of 0.9 (minutes)*

Neuromuscular Block Agent	Treatment Regimen	
	Rocuronium and Sugammadex (2.0 mg/kg)	Cis-atracurium and Neostigmine (50 micrograms / kg)
N	34	39
Median (minutes)	1.9	7.2
Interval	0.7–6.4	4.2–28.2

Emergence Reversal:
Time to recovery of succinylcholine-induced neuromuscular block (1.0 mg/kg) was compared to time to recovery of rocuronium-induced neuromuscular block with sugammadex (16 mg/kg, after 3 minutes) (1.2 mg/kg).

Table 6: *Time From Rocuronium or Sugammadex or Succinylcholine Administration to 10% T1 Recovery (minutes)*

Neuromuscular Block Agent	Treatment Regimen	
	Rocuronium and Sugammadex (16.0 mg/kg)	Succinylcholine(1 mg/kg)
N	55	55
Median (minutes)	4.2	7.1
Interval	3.5–7.7	3.7–10.5

In the unified analysis, the following response times in neuromuscular block were reported for 16 mg/kg sugammadex after 1.2 mg/kg rocuronium bromide:

Table 7*: Time to Recovery of T4/T1 Ratio of 0.9, 0.8, or 0.7 from Sugammadex Administration 3 Minutes After Rocuronium (minutes)*

	0.9 T4/T1	0.8 T4/T1	0.7 T4/T1
N	65	65	65
Median (minutes)	1.5	1.3	1.1
Interval	0.5–14.3	0.5–6.2	0.5–3.3

Renal Impairment:
The efficacy and safety of sugammadex were compared in two open-label studies in surgical patients with and without severe renal impairment. In one study, sugammadex (4 mg/kg; N=68) was administered following rocuronium-induced block in 1-2 PTCs; in the other study, sugammadex was administered when T2 reappeared (2 mg/kg; N=30). Recovery of neuromuscular block was slightly longer in patients with severe renal impairment compared

with patients without renal impairment. No residual or reoccurring neuromuscular block was reported for severe renal impairment in these studies.

Morbidly obese patients:
The recovery time from moderate or deep neuromuscular blockade caused by rocuronium or vek,uronium was investigated in a study involving 188 patients with a diagnosis of morbidly obese (body mass index ≥40 kg/m2). Patients dosed at random, double-blind, true body weight or ideal body weight according to the level of block received 2 mg/kg or 4 mg/kg sugammadex. In unified data by depth of block and neuromuscular blocking agent, a quadruple of 0.9 was found in patients dosed by actual body weight (1.8 minutes) compared with patients dosed according to ideal body weight (3.3 minutes). ($p<0.0001$).

Patients with severe systemic disease:
A study of 331 patients rated 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 (2mg/kg, 4mg/kg, or 16mg/kg), the incidence of treatment-emergent arrhythmias is usually neostigmine (50mcg/kg) compared to patients receiving neostigmine (50mcg/kg) to 5 mg max dose) + glycopyrrolate (10 mcg/kg to 1 mg max dose). The adverse reaction profile in ASA Class 3 and 4 patients was generally similar to that of adult patients in the pooled Phase 1 to 3 studies; therefore no dose adjustment is necessary (see section 4.8).

5.2. Pharmacokinetic properties

General Features

Absorption:
The pharmacokinetic parameters of sugammadex were calculated from the sum of the concentrations of complex-bound and unbound sugammadex. Pharmacokinetic parameters such as clearance and volume of distribution in anesthetized volunteers are considered to be the same for complex-dependent and uncomplex-dependent sugammadex.

Distribution:
The observed steady-state volume of distribution of sugammadex in adult patients with normal renal function is approximately 11-14 liters (based on classical, non-compartmental pharmacokinetic analysis). Neither sugammadex nor the sugammadex and rocuronium complex binds to plasma proteins or erythrocytes, as demonstrated in vitro using male human plasma and whole blood.

Biotransformation:
In preclinical and clinical studies, no metabolites of sugammadex were observed, and the product, as the elimination route, was only excreted unchanged by the kidney.

Elimination:
The effective half-life of sugammadex is approximately 2 hours and the calculated plasma clearance is approximately 88 mL/min in anesthetized adult patients with normal renal function. In a mass balance study, more than 90% of the dose was shown to be excreted within 24 hours. Of the dose contributing to sugammadex, at least 95% of which was excreted unchanged, 96% was excreted in the urine. Excretion in faeces or exhaled air is less than 0.02% of the dose. Administration of sugammadex to healthy volunteers resulted in increased renal elimination of rocuronium in the complex.

Linear/Non-linear case:
Sugammadex shows linear kinetics when administered as an IV bolus in the dose range of 1-16 mg/kg.

Characteristics in patients
Special populations:
Kidney impairment and age:
In two pharmacokinetic studies comparing patients with severe renal impairment and patients with normal renal function, sugammadex levels in plasma were similar for at least the first hour after dosing, after which levels decreased more rapidly in the control group. Total exposure time to sugammadex was prolonged, resulting in a 17-fold higher exposure in patients with severe renal impairment. In patients with severe renal impairment, low concentrations of sugammadex may be detected for at least 48 hours post-dose.

In a second study comparing patients with moderate or severe renal impairment with patients with normal renal function, the clearance of sugammadex gradually decreased as renal function decreased and the half-life (t1/2) progressively prolonged. The exposure was 2-fold and 5-fold higher, respectively, in patients with moderate or severe renal impairment. In patients with severe renal impairment, sugammadex concentrations became undetectable after 7 days post-dose.

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

Selected patient characteristics			**Predicted FK parameters**		
Demographic features	Renal function (creatinine clearance, mL/min)		Clearance, mL/min (CV)	Volume of distribution at steady state, liters	Effective half-life, hours
Adults 40 years old 75 kg	Normal	100	88 (22%)	12	2. (21%)
	Corrupted	Mild 50	(22%)	13	4 (22%)
		Middle 30	31 (23%)	14	6 (23%)
		Severe 10	9 (22%)	14	19 (24%)

Elderly 75 years 75 kg	Normal		80	75 (23%)	12	2. (22%)
	Corrupted	Mild	50	51(24%)	13	3 (22%)
		Middle	30	31 (23%)	14	6 (23%)
		Severe	10	9 (22%)	14	19 (23%)
Adolescent 15 years 56 kg	Normal		95	77 (23%)	9	2 (22%)
	Corrupted	Mild	48	44 (23%)	10	3 (22%)
		Middle	29	27 (22%)	10	5 (23%)
		Severe	10	8 (71%)	11	17 (23%)
Children 7 years 23 kg	Normal		51	37 (22%)	4	2 (20%)
	Corrupted	Mild	26	19 (22%)	4	3 (22%)
		Middle	15	11 (22%)	4	5 (22%)
		Severe	5	3 (22%)	5	20 (25%)

Mean and coefficient of variation (CV%) are presented

Gender:
No gender-related differences were observed.

Race:
In a study of healthy Japanese and Caucasian volunteers, no clinically significant differences in pharmacokinetic parameters were observed. Limited data do not indicate differences in pharmacokinetic parameters in black or African Americans.

Body Weight:
Population pharmacokinetic analysis of adult and elderly patients did not reveal a clinically relevant relationship between clearance and volume of distribution and body weight.

Obesity:
In a clinical study in morbidly obese patients, sugammadex was dosed at 2 mg/kg and 4 mg/kg based on actual body weight (n=76) or ideal body weight (n=74). Sugammadex exposure showed a dose-dependent, linear increase after administration relative to actual body weight or ideal body weight. No clinically significant difference in parameters was observed between morbidly obese patients and the general population.

5.3. Pre-clinical 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 eliminated in preclinical species, but residual sugammadex has been observed in the bones and teeth of young rats. Preclinical studies in young adult and mature rats

show that sugammadex does not adversely affect tooth color or bone quality, bone structure, or bone metabolism. Sugammadex has no effect on fracture repair and bone remodeling.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid 3.7% (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Compatibilities

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

6.3 Shelf Life

24 months
Product can be diluted with; 0.9% NaCl solution; 0.9% NaCl and 5% dextrose solution; 0.45% NaCl and 2.5% Dextrose solution; 5% Dextrose solution; Ringer's lactate solution and Ringer's solution.

After first opening and dilution, chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-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 generally not more than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions. The opened ampoule is for single use only and should be used immediately.

6.4 Special precautions for storage

Store at room temperature below 30°C.
Do not freeze.
The ampoule should be stored in the outer carton box to protect it from light.
See Section 6.3 for storage conditions of the diluted product.

6.5 Nature and contents of container

Single use injection contained in a heat-sealed hydrolytic resistant borosilicate type 1 Ph. Eur. glass funnel-ringed amber ampoule. The closure part is opened by breaking the ring marked place.

It is packaged in 2 mL amber (10 ampoules).

6.6 Special precautions for disposal and other handling

SUGAVER may be injected into continued intravenous infusion with the following intravenous

solutions: 9 mg/mL (0.9%) sodium chloride, glucose 50 mg/mL (5%), sodium chloride (5%), 4.5 mg/mL (0.45%), and glucose 25 mg/mL (5%) 2.5), Ringer's lactate solution, Ringer's solution, glucose (50 mg/mL) (5%) sodium chloride 9 mg/mL (0.9%)

Between administration of SUGAVER and other drugs, the intravenous line should be flushed appropriately (eg 0.9% sodium chloride).

Use in the pediatric population:
In pediatric patients, SUGAVER can be diluted to 10 mg/mL using sodium chloride 9 mg/ml (0.9%).

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION HOLDER

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9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

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Renewal date:

10. DATE OF REVISION OF THE TEXT