ACCODEX (SUGAMMADEX) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Sugammadex Solution for Injection 100mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 100 mg sugammadex (as sugammadex sodium)
2 mL contains 200 mg sugammadex (as sugammadex sodium)
5 mL contains 500 mg sugammadex (as sugammadex sodium)
For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Sugammadex solution for injection is a clear and colourless to slightly yellow-brown 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 patients 2 years of age and older.

4.2 DOSE AND METHOD 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.

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 4.0 mg/kg sugammadex is recommended if recovery has reached 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 Pharmacodynamic Properties, Clinical trials**).

A dose of 2.0 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to 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 Pharmacodynamic Properties, Clinical trials**).

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-induced blockade, when compared to vecuronium-induced neuromuscular blockade (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

Immediate reversal

If there is a clinical need for immediate reversal following administration of rocuronium, a dose of 16.0 mg/kg sugammadex is recommended. Administration of 16.0 mg/kg sugammadex 3 minutes following a bolus dose of 1.2 mg/kg rocuronium bromide provides a median time to recovery of the T_4/T_1 ratio to

0.9 of approximately 1.5 minutes (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

There are 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.

Paediatric population

Children and adolescents (2 years and older)

Sugammadex 100 mg/mL may be diluted to 10 mg/mL to increase the accuracy of dosing in the paediatric population (see **Method of administration**).

Routine reversal

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

A dose of 2 mg/kg is recommended for reversal of rocuronium or vecuronium-induced blockade at reappearance of T_2 (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

Immediate reversal

The use of higher doses (as for **immediate reversal**) in children and adolescents has not been investigated and is therefore not recommended.

Neonates and infants

There is only limited experience with infants (30 days to 2 years); neonates (less than 30 days) have not been studied. Therefore the use of sugammadex in neonates and infants is not recommended until further data become available.

Special populations

Renal impairment

The dose recommendations for mild and moderate renal impairment (creatinine clearance between 30 and 80 mL/min) are the same as for adults without renal impairment. For re-administration with rocuronium or vecuronium (see **Section 4.4 Special Warnings and Precautions for Use**) for waiting times.

Sugammadex is not recommended for use in patients with severe renal impairment (including patients requiring dialyses) (see **Section 4.4 Special Warnings and Precautions for Use**). Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of sugammadex in these patients (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

Hepatic impairment

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

Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of sugammadex in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see Section 4.4 Special Warnings and Precautions for Use).

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) it was 3.6 minutes. Even though the recovery time in elderly tends to be slower, the same dose recommendation as for adults should be followed (see **Section 4.4 Special Warnings and Precautions for Use**).

Obese patients

In obese patients, including morbidly obese patients, the dose of sugammadex should be based on actual body weight. The same dose recommendation as for adults should be followed.

Method of administration

Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, into an existing IV line. Sugammadex has only been administered as a single bolus injection in clinical trials.

Compatibility

Sugammadex can be injected into the intravenous line of a running infusion with the following intravenous solutions: 0.9% sodium chloride; 5% glucose, Gelofusine; 0.45% sodium chloride and 2.5% glucose; Ringers lactate solution; Ringers solution; Lactec; Lactec D and G; Hespander; Veen-F; Physio 140; 5% glucose in 0.9% sodium chloride; and isolyte P with 5% glucose.

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

For *paediatric patients,* Sugammadex can be diluted using 0.9% sodium chloride to a concentration of 10 mg/mL.

After dilution with infusion fluids, to reduce microbiological hazard, the diluted solution should be used as soon as practical. If storage of the diluted solution is necessary, solutions should be stored at room temperature (below 25°C) for no more than 6 hours or under refrigeration at 2°C to 8°C for no more than 24 hours.

The product contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Waiting times for re-administration with neuromuscular blocking agents after reversal with sugammadex

If re-administration of rocuronium or vecuronium is required after reversal with sugammadex (up to 4 mg/kg), the following waiting times are recommended (see Table 1).

Table 1: In patients with normal renal function (creatinine clearance >80 mL/min)

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

Based on PK modelling the recommended waiting time in patients with mild or moderate renalimpairment for re-use of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after routine reversalwith 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.

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

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 fractionof postjunctional nicotinic receptors can still be occupied by the neuromuscular blocking agent.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Immediate reversal

There are no data for immediate reversal following vecuronium blockade (see **Section 4.2 Dose and Method of Administration**).

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 drugs used in the peri- and postoperative period could depress respiratory function and therefore ventilatory support might still be required. Should neuromuscular blockade recur 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 (N=2022), an incidence of 0.2% 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 Dose and Method of Administration** and **Section 4.8 Adverse Effects (Undesirable Effects)**).

Effect on haemostasis

In a study of volunteers, doses of 4 mg/kg and 16 mg/kg of sugammadex resulted in maximum mean prolongations of activated partial thromboplastin time (aPTT) by 17 and 22%, respectively and of prothrombin time international normalised ratio (PT(INR)) by 11 and 22%, respectively. These limited mean aPPT and PT(INR) prolongations were of short duration (≤ than 30 minutes). Although there is limited data on peri- or postoperative bleeding events in the clinical trial database (N=3519), there is no indication of a clinically relevant increased incidence of bleeding events after sugammadex alone, or after sugammadex in combination with anticoagulants.

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

In *in vitro* experiments additional aPPT and PT prolongation was noted for sugammadex in combination with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran. Considering the transient nature of the limited prolongation of aPTT and PT caused by sugammadex alone or on top of these anticoagulants, it is unlikely that sugammadex had an increased risk of bleeding.

Since bleeding risk has not been studied systematically at higher doses than sugammadex 4 mg/kg, coagulation parameters should be carefully monitored in patients using anticoagulants who receive a dose of 16 mg/kg sugammadex. Since there is no information on the use of sugammadex in patients with known coagulopathies, it is recommended that these patients have their aPTT, PT and PT (INR) monitored after administration of sugammadex.

Interactions due to the lasting effect of rocuronium or vecuronium

When drugs which potentiate neuromuscular blockade are used in the post-operative period, special attention should be paid to the possibility of recurrence of blockade. Please refer to the Product Information for rocuronium or vecuronium for a list of the specific drugs 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 Dose and method of administration).

Potential interactions

- Capturing interactions:

Due to the administration of sugammadex, certain medicinal products could become less effective due to a lowering of the (free) plasma concentrations (see section 4.5, hormonal contraceptives).

If such a situation is observed, the clinician is advised to consider the re-administration of the medicinal product, the administration of a therapeutically equivalent medicinal product (preferably from a different chemical class) and/or non-pharmacological interventions as appropriate.

- Displacement interactions:

Due to the administration of certain medicinal products after sugammadex, theoretically rocuronium or vecuronium could be displaced from sugammadex. Displacement interactions are at present only expected for a few drug substances (toremifene and fusidic acid, see section 4.5). As a result recurrence of neuromuscular blockade might be observed. In this situation the patient must be ventilated. Administration of the medicinal product which caused displacement should be stopped in case of an infusion. In situations when potential displacement interactions can be anticipated, patients should be carefully monitored for signs of recurrence of neuromuscular blockade (approximately up to 15 minutes) after parenteral administration of another medicinal product occurring within a period of 7.5 hours after sugammadex administration.

Anaesthetic complication

When neuromuscular blockade was reversed in the middle of anaesthesia in clinical trials, i.e. when investigating immediate reversal, 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 (see **Section 4.8 Adverse Effects (Undesirable Effects)**).

Marked bradycardia

In rare instances, marked bradycardia has been observed within minutes after administration of sugammadex for reversal of neuromuscular blockade. Isolated cases of bradycardia with cardiac arrest have been reported (see **Section 4.8 Adverse Effects (Undesirable Effects)**). 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.

Use in ICU

Sugammadex has not been investigated in the ICU setting.

Use for reversal of neuromuscular blocking agents other than rocuronium or vecuronium

Sugammadex should not be used to reverse blockade induced by nonsteroidal neuromuscular blocking agents such as suxamethonium 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 sugammadex is not recommended to reverse blockade induced with pancuronium.

Delayed recovery

Conditions associated with prolonged circulation time such as cardiovascular disease, old age (see **Section 4.2 Dose and Method of Administration**), or oedematous state (e.g. severe hepatic impairment) may be associated with longer recovery times.

Drug hypersensitivity

Clinicians should be prepared for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions. The risk of drug hypersensitivityreactions appears to be dose-dependent (**see Section 5.1 Pharmacodynamic Properties, Clinical trials** and **Section 4.8 Adverse Effects (Undesirable Effects)**).

Use in hepatic impairment

Sugammadex is not metabolised or excreted by the liver; therefore dedicated 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 **Effect on haemostasis**).

Use in renal impairment

Sugammadex is not recommended for use in patients with severe renal impairment, includingthose requiring dialysis (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

Use in the elderly

See **Section 4.2 Dose and Method of Administration, Special populations, Elderly patients; Section 5.2 Pharmacokinetic Properties, Special populations**.

Paediatric use

- Sugammadex should not be given to children aged less than 2 years.
- Efficacy and safety of sugammadex for immediate reversal in children have not been assessed.

Patients on a controlled sodium diet

Each ml solution contains 9.7 mg sodium. A dose of 23 mg sodium is considered essentially 'sodium-free'. If more than 2.4 ml solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Sugammadex has no potential to cause drug-drug interaction due to inhibition or induction of drug

metabolising enzymes. The mechanism of potential drug-drug interaction is through binding of sugammadex to other compounds, which cannot be assessed via traditional drug- drug interaction studies. Therefore a combined strategy (based on binding affinity between sugammadex and other drugs, pre-clinical experiments, simulations of a Pharmacokinetic- Pharmacodynamic (PK - PD) model and clinical studies) was applied to assess both the capturing and displacement interactions. Based on these data, no clinically significant pharmacodynamic interactions with other drugs are expected, with the exception of toremifene, fusidic acid and hormonal contraceptives (see below). For these drugs a clinically relevant interaction could not be excluded.

No clinically relevant interactions were reported during clinical development in approximately 1700 patients.

Effects on laboratory tests

In general sugammadex does not interfere with laboratory tests, with the possible exception of the serum progesterone assay. Interference with this test was observed at sugammadex plasma concentrations of 100 µg/mL, which is in the same range as C_{max} values observed after a dose of 16 mg/kg.

Paediatric population

No formal interaction studies have been performed. The interactions for adults and the warnings should also be taken into account for the paediatric population (see **Section 4.4 Special Warnings and Precautions for Use**).

Interactions potentially affecting the efficacy of sugammadex

Displacement interactions

Due to the administration of certain drugs 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 orrocuronium from the complex with sugammadex could occur. The recovery of the T_4/T_1 ratio to 0.9 could therefore be delayed in patients who have received toremifene on the same day of the operation.

Intravenous administration of fusidic acid

The use of fusidic acid in the pre-operative phase may give some delay in the recovery of T_4/T_1 ratio to 0.9. However, no recurrence of neuromuscular blockade is expected in the post-operative phase, since the infusion rate of fusidic acid is over a period of several hours and the blood levels are cumulative over 2-3 days.

Flucloxacillin

Based on the binding affinity of sugammadex for flucloxacillin and PK modelling, it could not be excluded that high doses of flucloxacillin might cause some displacement of rocuronium orvecuronium from sugammadex causing some delay in the recovery for the T_4/T_1 ratio to 0.9. However, in 6 healthy male and female volunteers (age <45y - mean 33y; mean weight 75 kg)no evidence of reoccurrence of neuromuscular blocking was seen using adductor pollicis acceleromyography (TOF® SX). Based on

these results, it may be concluded that the displacement potential by flucloxacillin is not clinically relevant.

Interactions potentially affecting the efficacy of other drugs

Capturing interactions

Due to the administration of sugammadex, certain drugs could become less effective due to alowering of the (free) plasma concentrations. Theoretically, for certain drugs (acute) withdrawal effects could also be expected after administration of sugammadex.

When such a situation (reduced effect and/or withdrawal effect) is observed, the clinician is advised to consider the re-administration of the drug, the administration of a therapeutically equivalent drug (preferably from a different chemical class) and/or non-pharmacological interventions as appropriate.

Hormonal contraceptives

In a simulation performed with a PK/PD model, it was found that the interaction between 4 mg/kg sugammadex and a progestogen could lead to a decrease in progestogen exposure (34% of AUC) similar to the decrease seen when a daily dose of an oral contraceptive is taken12 hours too late, which might lead to a reduction in effectiveness. For estrogens the effect is expected to be lower. Therefore the administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of **oral** contraceptive steroids (either combined or progestogen only). Refer to the missed dose advice in the package insert of theoral contraceptive for any actions required if an oral contraceptive is taken on the same day that sugammadex is administered.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Sugammadex at doses of up to 500 mg/kg/day did not affect fertility in rats. This dose resulted in a drug exposure (AUC) that was 28-fold that in humans with the single 4 mg/kg dose.

Use in pregnancy

There are no clinical data for exposed pregnancies. In animal studies with administration over the whole period of organogenesis, sugammadex did not affect foetal development at doses resulting in drug exposures (AUC) that were 28-fold (rats) and 31-fold (rabbits) that in humans with the single 4 mg/kg dose. A maternotoxic dose in rabbits (drug exposure 32-fold that in humans with the single 4 mg/kg dose) resulted in reduced foetal weight and impaired skeletal ossification. Because animal studies are not always predictive of human responses, sugammadex should be used in pregnant women only when the benefits outweigh potential effects on the foetus.

Use in lactation

It is not known if sugammadex is excreted in human milk, but excretion in rat milk has been demonstrated. Rat offspring development was unaffected by oral exposure via the milk in a pre- and post-natal development study.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Sugammadex has no known influence on the ability to drive and use machines. The usual precautionary measures after a general anaesthetic should be taken for ambulatory patients.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

In the subset of Pooled Placebo-controlled trials where subjects received anaesthesia and/or neuromuscular blocking agents (1078 subject exposures to sugammadex versus 544 to placebo), the following adverse events occurred in ≥2% of subjects treated with sugammadex.

Table 2: Adverse events by MedDRA System Organ Class (SOC) and Preferred Term (PT) in at least 2% of sugammadex treated subjects in pooled phase 1-3 placebo-controlled trials where subjects received anaesthesia and/or neuromuscular blocking agent

MedDRA 17.0		Rocuronium or vecuronium +	
		Total Sugammadex[a]	Placebo
		(N=1078)	(N=544)
System Organ class	Adverse Reaction (Preferred Term)		
		n (%)	n (%)
At least one AE	Total	793 (73.6)	447 (82.2)
Injury, poisoning and procedural complications	Total	455 (42.2)	280 (51.5)
	Procedural pain	268 (24.9)	191 (35.1)
	Wound complication	71 (6.6)	32 (5.9)
	Anaemia postoperative	54 (5.0)	51 (9.4)
	Airway complication of anaesthesia	42 (3.9)	0 (0.0)
	Anaesthetic complication	37 (3.4)	1 (0.2)
	Procedural hypotension	36 (3.3)	9 (1.7)
	Post procedural complication	32 (3.0)	24 (4.4)
	Procedural hypertension	25 (2.3)	22 (4.0)
	Procedural complication	22 (2.0)	3 (0.6)
	Procedural vomiting	22 (2.0)	14 (2.6)
	Wound secretion	22 (2.0)	19 (3.5)
Gastrointestinal disorders	Total	310 (28.8)	195 (35.8)
	Nausea	169 (15.7)	96 (17.6)
	Vomiting	100 (9.3)	43 (7.9)
	Constipation	74 (6.9)	73 (13.4)
	Diarrhoea	23 (2.1)	22 (4.0)
General disorders and administration site conditions	Total	216 (20.0)	117 (21.5)
	Pain	51 (4.7)	16 (2.9)
	Pyrexia	44 (4.1)	17 (3.1)
	Chills	41 (3.8)	27 (5.0)
	Oedema peripheral	36 (3.3)	23 (4.2)
Musculoskeletal and connective tissue disorders	Total	143 (13.3)	103 (18.9)
	Arthralgia	47 (4.4)	42 (7.7)
	Back pain	34 (3.2)	22 (4.0)
Respiratory, thoracic and mediastinal disorders	Total	130 (12.1)	51 (9.4)
	Cough	51 (4.7)	11 (2.0)
	Oropharyngeal pain	38 (3.5)	27 (5.0)
Nervous system disorders	Total	111 (11.3)	87 (16.0)
	Headache	53 (4.9)	42 (7.7)

Investigations	Total	112 (10.4)	33 (6.1)
Psychiatric Disorders	Total	100 (9.3)	89 (16.4)
	Sleep Disorder	45 (4.2)	56 (10.3)
	Insomnia	36 (3.3)	22 (4.0)
Vascular disorders	Total	88 (8.2)	60 (11.0)
	Haematoma	28 (2.6)	26 (4.8)
	Hypotension	26 (2.4)	11 (2.0)
Renal and urinary disorders	Total	62 (5.8)	40 (7.4)
Blood and lymphatic system disorders	Total	58 (5.4)	54 (9.9)
	Anaemia	47 (4.4)	50 (9.2)
Metabolism and nutrition disorders	Total	56 (5.2)	39 (7.2)
Skin and subcutaneous tissue disorders	Total	55 (5.1)	38 (7.0)
Infections and infestations	Total	52 (4.8)	37 (6.8)
Cardiac disorders	Total	40 (3.7)	27 (5.0)
Ear and labyrinth disorders	Total	25 (2.3)	11 (2.0)

N = Number of subject exposures per treatment group; AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities

[a] Total Column includes subjects exposed to all doses of intravenous sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20, or 32 mg/kg).
Notes: This table includes AEs that occurred in at least 2% of sugammadex subjects whether summarised by SOC or by PT. If a SOC is listed with no subordinate PT, there was no subordinate PTin that SOC that occurred in at least 2% of sugammadex subjects.

For the adverse events listed in Table 2, only cough, airway complication of anaesthesia, anaesthetic complication, procedural hypotension and procedural complication occurred at least twice as often in subjects treated with sugammadex compared to placebo.

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

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 contra breath (spontaneous breath of patient, anaesthetic procedure related).

Anaesthetic complication

This complication, indicative of the restoration of neuromuscular function (movement of a limb or the body or coughing during anaesthetic procedure or during surgery, grimacing or suckling on the endotracheal tube), was judged to be related to treatment with sugammadex in about 3% of the patients and <1% of the placebo group. Most occurrences of anaesthetic complications were mild to moderate.

Procedural complication

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

Description of selected adverse reactions

The following adverse reactions were biologically plausible irrespective of incidence, or for which a causal relationship could not be excluded and which could be clinically relevant in theanticipated setting.

Recurrence of neuromuscular blockade

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade (N=2022), an incidence of 0.20% was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring

or clinical evidence (see **Section 4.4 Special Warnings and Precautions for Use**).

Drug hypersensitivity reactions

Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and healthy volunteers. In clinical trials, of surgical patients, these reactions were reported uncommonly (≥ 1/1000 to < 1/100) and for post-marketing reports the frequency is unknown. These reactions varied from isolated skin reactions to serious systemicreactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to sugammadex.

Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash,(severe) hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal.

Information on healthy volunteers

A randomised, double-blind study examined the incidenceof drug hypersensitivity reactions in healthy volunteers given up to 3 repeat 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 afterplacebo 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 increasedfrequency or severity of hypersensitivity with repeat dosing of sugammadex.

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

The most common adverse reaction in pooled healthy volunteers was dysgeusia (10%).

Marked bradycardia

In post-marketing, isolated cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex (see **Section 4.4 Special Warnings and Precautions for Use**).

Pulmonary patients

In post-marketing data and in one dedicated clinical trial in patients with a history of pulmonary complications (see **Section 5.1 Pharmacodynamic Properties, Clinical Trials**), bronchospasm was reported as a possibly related adverse event. As with all patients with a history of pulmonary complications the physician should be aware of the possible occurrence of bronchospasm.

Paediatric population

A limited database suggests that the safety profile of sugammadex (up to 4 mg/kg) in paediatric patients was similar to that in adults.

Morbidly obese patients (BMI≥40 kg/m^2)

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

Patients with severe systemic disease:

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

4.9 OVERDOSE

In clinical studies, 1 case of an accidental overdose with 40 mg/kg was reported without any significant side effects. In a human tolerance study sugammadex was well tolerated in doses up to 96 mg/kg. Sugammadex can be removed using haemodialysis with a high flux filter. Based upon clinical studies,

sugammadex concentrations in plasma are reduced with a high flux filter by about 70% after a 3-6 hour dialysis session.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Sugammadex is a modified gamma cyclodextrin which is a Selective Relaxant Binding Agent (SRBA). It forms a complex with the neuromuscular blocking agents rocuronium or vecuronium and it reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium 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 trials

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 T4/T1 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

Neuromuscularblocking agent	**Treatment regimen**	
	Sugammadex (4.0 mg/kg)	Neostigmine (70 mcg/kg)
Rocuronium		
N	37	37
Median (minutes)	2:7	49.0
Range	1.2 – 16.1	13.3 – 145.7
Vecuronium		
N	47	36
Median (minutes)	3.3	49.9
Range	1.4 – 68.4	46.0 – 312.7

Routine reversal – moderate neuromuscular blockade

In another pivotal study patients were randomly assigned to the rocuronium or vecuronium group. After the last dose of rocuronium or vecuronium, at the reappearance of T2, 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 T4/T1 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	**Treatment regimen**

agent	Sugammadex (2.0 mg/kg)	Neostigmine (50 mcg/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)	2:08	18:56
Range	1:12 - 64:12	2:55 - 76:09

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 T2 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 (2.0 mg/kg)	Cis-atracurium and Neostigmine (50 mcg/kg)
N	34	39
Median (minutes)	1.9	7.2
Range	0.7 – 6.4	4.2 – 28.2

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 (min:sec) from administration of rocuronium or suxamethonium to recovery of T_1 10%

Neuromuscular blocking agent	**Treatment regimen**	
	Rocuronium and Sugammadex (16.0 mg/kg)	Suxamethonium (1.0 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

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

Effects on QTc-interval

In three dedicated clinical studies (N=287) sugammadex alone, sugammadex in combination with rocuronium or vecuronium and sugammadex in combination with propofol or sevoflurane was not

associated with clinically relevant QT/QTc prolongation. The integrated ECG and adverse event results of phase 2-3 studies support this conclusion.

Morbidly obese patients

A trial of 188 adult patients who were diagnosed as morbidly obese (body mass index ≥ 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. Pooled across depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio ≥ 0.9 in patients dosed by actual body weight (1.8 minutes) was statistically significantly faster ($p < 0.0001$) compared to patients dosed by ideal body weight (3.3 minutes).

Patients with severe systemic disease

A trial of 331 patients who were assessed as ASA Class 3 or 4 investigated the incidence of treatment-emergent arrhythmias (sinus bradycardia, sinus tachycardia, or other cardiac arrhythmias) after administration of sugammadex.

In patients receiving sugammadex (2 mg/kg, 4 mg/kg, or 16 mg/kg), the incidence of treatment-emergent arrhythmias was generally similar to neostigmine (50 µg/kg up to 5 mg

maximum dose) + glycopyrrolate (10 µg/kg up to 1 mg maximum dose). The percentage of patients with treatment-emergent sinus bradycardia was significantly lower (p=0.026) in the sugammadex 2 mg/kg group compared with the neostigmine group. The percentage of patients with treatment-emergent sinus tachycardia was significantly lower in the sugammadex 2 mg/kg and 4 mg/kg groups compared with the neostigmine group (p=0.007 and 0.036, respectively). The safety profile in ASA Class 3 and 4 patients was generally similar to that of adult patients in pooled Phase 1 to 3 studies; therefore, no dosage adjustment is necessary. See section 4.8.

Paediatric Population

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

5.2 PHARMACOKINETIC PROPERTIES

The sugammadex pharmacokinetic parameters were calculated from the total sum of non- complex and complex-bound concentrations of sugammadex. Pharmacokinetic parameters as clearance and volume of distribution are assumed to be the same for non-complex-bound and complex-bound sugammadex in anaesthetised subjects.

Distribution

The observed steady-state volume of distribution of sugammadex is approximately 11 to 14 litres in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Neither sugammadex nor the complex of sugammadex and rocuronium bind 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

The elimination half-life ($t_{1/2}$) of sugammadex in adult anaesthetised patients with normal renal function is about 2.0 hours and plasma clearance is estimated to be 88 mL/min. A mass balance study demonstrated that > 90% of the dose was excreted within 24 hours. Overall 96% of the dose was excreted in the 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. Total exposure to sugammadex was prolonged, leading to 17-fold higher exposure in patients with severe renal impairment. Low concentrations of sugammadex are detectable for at least 48 hours post-dose in patients with severe renal insufficiency.

In a second study comparing subjects with moderate or severe renal impairment to subjects with normal renal function, sugammadex clearance progressively decreased and $t_{1/2}$ was progressively prolonged with declining renal function. Exposure was 2-fold and 5-fold higher in subjects with moderate and severe renal impairment, respectively. Sugammadex concentrations were no longer detectable beyond 7 days post-dose in subjects with severe renal insufficiency.

A summary of sugammadex pharmacokinetic parameters stratified by age and renal functionis presented in Table 8.

Table 8: Pharmacokinetic Parameters of Sugammadex Based on Population Pharmacokinetic Modelling in Children to Elderly by Renal Function

Selected patient characteristics				Mean predicted PK parameters (CV*%)		
Demographics	Renal function Creatinine clearance (mL/min)			Clearance (mL/min)	Volume of distribution at steady state (L)	Elimination half-life (hr)
Adult	Normal		100	84 (24)	13	2 (22)
40 yrs	Impaired	Mild	50	47 (25)	14	4 (22)
75 kg		Moderate	30	28 (24)	14	7 (23)
		Severe	10	8 (25)	15	24 (25)
Elderly	Normal		80	70 (24)	13	3 (21)
75 yrs	Impaired	Mild	50	46 (25)	14	4 (23)
75 kg		Moderate	30	28 (25)	14	7 (23)
		Severe	10	8 (25)	15	24 (24)
Adolescent	Normal		95	72 (25)	10	2 (21)
15 yrs	Impaired	Mild	48	40 (24)	11	4 (23)
56 kg		Moderate	29	24 (24)	11	6 (24)
		Severe	10	7 (25)	11	22 (25)
Middle	Normal		60	40 (24)	5	2 (22)
childhood	Impaired	Mild	30	21 (24)	6	4 (22)
9 yrs		Moderate	18	12 (25)	6	7 (24)
29 kg		Severe	6	3 (26)	6	25 (25)
Early	Normal		39	24 (25)	3	2 (22)
childhood	Impaired	Mild	19	11 (25)	3	4 (23)
4 yrs		Moderate	12	6 (25)	3	7 (24)

16 kg		Severe	4	2 (25)	3	28 (26)

*CV=coefficient of variation

Pediatric Patients:

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

Sugammadex exposure (AUC0-inf and Cmax) increased in a dose-dependent, linear manner following administration of 2 and 4 mg/kg across patients 2 to <17 years of age. Sugammadex exposure was approximately 40% lower in patients 2 to <6 years of age following administration of 2 or 4 mg/kg sugammadex compared to older pediatric patients (6 to <17 years) and adults; however, this difference was not clinically relevant [see section 5.1].

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

Gender

No gender differences were observed.

Race

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

Body weight

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

Obesity

In one clinical study in morbidly obese adult 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 normal adults.

5.3 PRECLINICAL SAFETY DATA

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

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

Sugammadex is rapidly cleared in preclinical species, although residual sugammadex was observed in bone and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex does not adversely affect tooth 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 Injections

6.2 INCOMPATIBILITIES

Sugammadex must not be mixed with other medical products except those mentioned in **Section 4.2Dose and Method of Administration, Compatibility**. The infusion line should be adequately flushed (e.g. with 0.9% sodium chloride) between administration of Sugammadex and other drugs.

Physical incompatibility was observed with verapamil, ondansetron and ranitidine.

6.3 SHELF LIFE

2 years

Refer to **Section 4.2 Dose and Method of Administration (Compatibility)** for shelf life of diluted solutions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC. Do not freeze. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Sugammadex is available in the following pack sizes: 200 mg/2 mL and 500 mg/5 mL, in Type I clear glass vials, with a stopper and flip-off top in packs of 10.

Not all pack-sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 NAME AND ADDRESS OF PRODUCT REGISTRANT

Accord Healthcare Private Limited
6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

8 DATE OF REVISION OF PACKAGE INSERT

Apr 2024