47.5 mm

Front

Pharmacode

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Madex

Sugammadex Solution for Injection 100 mg/ml

PRODUCT DESCRIPTION

Madex is Clear, colorless to slightly yellow solution packed in 2ml vial in a carton along with leaflet. Free from foreign matter.
Description after dilution: Clear colorless to slightly yellow- brown solution.
Sugammadex solution for Injection contains approx. 9.19 mg sodium per ml.

PHARMACODYNAMICS

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

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

Pharmacodynamic effects:
Sugammadex has been administered in doses ranging from 0.5 mg/kg to 16 mg/kg in dose response studies of rocuronium induced blockade (0.6, 0.9, 1.0 and 1.2 mg/kg rocuronium bromide with and without maintenance doses) and vecuronium induced blockade (0.1 mg/kg vecuronium bromide with or without maintenance doses) at different time points/depths of blockade. In these studies a clear dose-response relationship was observed.

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

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

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

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

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

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

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

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

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

Neuromuscular blocking agent	Treatment regimen	
	Rocuronium and sugammadex (2 mg/kg)	Cis-atracurium and neostigmine (50 mcg/kg)
N	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).

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

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

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

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

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

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

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

Morbidly obese patients:
A trial of 188 patients who were diagnosed as morbidly obese (body mass index ≥ 40 kg/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 adverse reaction profile in ASA Class 3 and 4 patients was generally similar to that of adult patients in pooled Phase 1 to 3 studies; therefore, no dosage adjustment is necessary.

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

Birth to <2 years of age:
Time to recovery from neuromuscular blockade induced by rocuronium or vecuronium followed by administration of Sugammadex or neostigmine was assessed in a randomized, double blind, active comparator-controlled study. The study was conducted in 145 randomized pediatric patients from birth to <2 years of age, of which 138 patients received treatment (92 boys and 46 girls; ASA class 1, 2, and 3; 68% were White; median weight was 5.8 kg; median age was 100.5 days). The primary efficacy objective was to evaluate the time to neuromuscular recovery of Sugammadex in comparison to neostigmine for the reversal of moderate neuromuscular blockade.
Time to neuromuscular recovery was statistically significantly faster in participants dosed with Sugammadex 2 mg/kg (N=29) compared with neostigmine (N=31) (median of 1.4 minutes for Sugammadex 2 mg/kg and 4.4 minutes for neostigmine; hazard ratio=2.40, 95% CI: 1.37, 4.18). Sugammadex 4 mg/kg achieved neuromuscular recovery with a median of 1.1 minutes. These effects were consistent across age cohorts studied (birth to 27 days, 28 days to <3 months, 3 months to <6 months, 6 months to <2 years of age).

PHARMACOKINETIC PROPERTIES

The sugammadex pharmacokinetic parameters were calculated from the total sum of non-complex-bound 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 anesthetized subjects.

Distribution:
The observed steady-state volume of distribution of sugammadex is approximately 11 to 14 litres in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Neither sugammadex nor the complex of sugammadex and rocuronium binds to plasma proteins or erythrocytes, as was shown in vitro using male human plasma and whole blood. Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose.

Metabolism:
In preclinical and clinical studies no metabolites of sugammadex have been observed and only renal excretion of the unchanged product was observed as the route of elimination.

Elimination:
In adult anesthetized patients with normal renal function the elimination half-life ($t_{½}$) of sugammadex is about 2 hours and the estimated plasma clearance is about 88 ml/min. A mass balance study demonstrated that > 90 % of the dose was excreted within 24 hours. 96 % of the dose was excreted in urine, of which at least 95 % could be attributed to unchanged sugammadex. Excretion via feces or expired air was less than 0.02 % of the dose. Administration of sugammadex to healthy volunteers resulted in increased renal elimination of rocuronium in complex.

Special populations:
Renal impairment and age:
In a pharmacokinetic study comparing patients with severe renal impairment to patients with normal renal function, sugammadex levels in plasma were similar during the first hour after dosing and thereafter the levels decreased faster in the control group. Total exposure to sugammadex was prolonged, leading to 17-fold higher exposure in patients with severe renal impairment. Low concentrations of sugammadex are detectable for at least 48 hours post- dose in patients with severe renal insufficiency.
In a second study comparing subjects with moderate or severe renal impairment to subjects with normal renal function, sugammadex clearance progressively decreased and $t_{1/2}$ was progressively prolonged with declining renal function. Exposure was 2-fold and 5-fold higher in subjects with moderate and severe renal impairment, respectively. Sugammadex concentrations were no longer detectable beyond 7 days post-dose in subjects with severe renal insufficiency.

Summary of sugammadex pharmacokinetic parameters stratified by age and renal function

Selected Patient Characteristics				Mean Predicted PK Parameters (CV*%)		
Demographics Age Body Weight	Renal function creatine clearance (mL/min)			Clearance (mL/min)	Volume of distribution at steady state (L)	Elimination half-life (h)
Adult	Normal		100	84 (26)	13	2.2 (23)
40 years 75 kg	Impaired	Mild	50	48 (28)	15	4.1 (25)
		Moderate	30	29 (28)	15	7.0 (26)
		Severe	10	8.9 (27)	16	23 (27)
Elderly	Normal		80	73 (27)	13	2.6 (25)
75 years 75 kg	Impaired	Mild	50	48 (27)	15	4.1 (25)
		Moderate	30	29 (26)	15	6.9 (25)
		Severe	10	8.9 (28)	16	23 (27)
Adolescent	Normal		95	71 (27)	10	2.0 (23)
15 years 56 kg	Impaired	Mild	48	41 (28)	11	3.8 (25)
		Moderate	29	25 (28)	12	6.3 (25)
		Severe	9.5	7.4 (28)	12	22 (28)
Middle Childhood	Normal		60	39 (29)	5.8	2.1 (24)
9 years 28 kg	Impaired	Mild	30	21 (27)	6.3	4.0 (25)
		Moderate	18	12 (28)	6.5	6.8 (26)
		Severe	6.0	3.3 (28)	6.7	25 (27)
Early Childhood	Normal		37	22 (26)	3.4	2.1 (24)
3.5 years 15 kg	Impaired	Mild	18	11 (28)	3.5	4.2 (25)
		Moderate	11	6.1 (27)	3.6	7.6 (27)
		Severe	3.7	1.6 (27)	3.7	28 (27)
Toddler	Normal		28	16 (28)	2.5	2.1 (24)
1.5 years 11 kg	Impaired	Mild	14	7.6 (28)	2.5	4.4 (26)
		Moderate	8.4	4.2 (28)	2.6	7.9 (28)
		Severe	2.8	1.1 (27)	2.6	29 (27)
Infant	Normal		21	12 (28)	1.8	2.2 (24)
6 months 7.9 kg	Impaired	Mild	11	5.4 (27)	1.9	4.6 (26)
		Moderate	6.4	2.9 (26)	1.9	8.3 (26)
		Severe	2.1	0.76 (28)	1.9	32 (27)
Neonate	Normal		13	13 (28)	1.1	1.3 (22)
15 days 3.8 kg	Impaired	Mild	6.4	5.7 (26)	1.1	2.7 (23)
		Moderate	3.9	3.1 (27)	1.1	4.8 (26)
		Severe	1.3	0.77 (27)	1.1	18 (26)

*CV=coefficient of variation

Gender:
No gender differences were observed.

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

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

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

INDICATIONS

Madex is indicated for the reversal of neuromuscular blockage induced by rocuronium bromide and vecuronium bromide in adult and pediatric patients undergoing surgery.

DOSAGE & 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 anesthetic regimen.Sugammadex can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade:

Adults

Routine reversal:
A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 3 minutes. A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 2 minutes. Using the recommended doses for routine reversal will result in a slightly faster median time to recovery of the T_4/T_1 ratio to 0.9 of rocuronium when compared to vecuronium induced neuromuscular blockade.

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

Re-administration of sugammadex:
In the exceptional situation of recurrence of neuromuscular blockade post- operatively 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 Special warnings and precautions for use.

Additional information on special population
Renal impairment:
For mild and moderate renal impairment (creatinine clearance ≥ 30 and < 80 ml/min): the dose recommendations are the same as for adults without renal impairment.
The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis (CrCl < 30 ml/min)) is not recommended.
Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of sugammadex in these patients.

Elderly patients:
After administration of sugammadex at reappearance of T_2 following a rocuronium induced blockade, the median time to recovery of the T_4/T_1 ratio to 0.9 in adults (18-64 years) was 2.2 minutes, in elderly adults (65-74 years) it was 2.6 minutes and in very elderly adults (75 years or more) it was 3.6 minutes. Even though the recovery times in elderly tend to be slower, the same dose recommendation as for adults should be followed.

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

Hepatic impairment:
For mild to moderate hepatic impairment: as sugammadex is mainly excreted renally no dose adjustments are required.
Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of sugammadex in patients with severe hepatic impairment is accompanied by coagulopathy.

Preparation of dilution for pediatric use:
Madex 100 mg/mL may be diluted to a concentration of 10 mg/mL, using 0.9% sodium chloride injection, USP, to increase the accuracy of dosing in the pediatric population.

- To prepare the required dose, aseptically transfer all the contents of the 2 mL vial of Madex 2-mL single-dose vials containing 200 mg sugammadex (100 mg/mL) to a bottle (or intravenous bag) containing 18 mL of 0.9% sodium chloride injection, to achieve a final concentration of 10 mg/mL sugammadex. The diluted solution should be used immediately.
- Madex injection is a single-dose sterile solution without preservatives. Discard any unused portion from the vial.

Pediatric population (birth and older) for reversal of rocuronium and vecuronium induced neuromuscular blockade:
Sugammadex 100 mg/ml may be diluted to 10 mg/ml to increase the accuracy of dosing in the pediatric population.

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) and there are no twitch responses to train-of-four (TOF) stimulation.
A dose of 2 mg/kg is recommended for reversal of rocuronium or vecuronium induced blockade at reappearance of T_2.

Immediate reversal:
Immediate reversal has not been investigated in the pediatric population.

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

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients

WARNINGS AND PRECAUTION

Monitoring respiratory function during recovery:

560 mm

190 mm

USV Private Limited					
Market/Country : Malaysia	**Co-ordinator Name :** Sachin			**Software :** Illustrator	
SAP Code : 3018XXX	**Item type :** Packinsert	**Date:** 08/10/2025		**Version :** 2025	
				Artist Name : Ajay	
Product Name : Madex (Sugammadex injection 100 mg/mL)					
Actual Size : 190 mm x 560 mm (L x H) Front & Back			**Reference SAP Code :** 3018462		
Pharmacode : ---			**Layout No.** -----		
CMYK/Pantone : Black	**Font -** Times New Roman	**Size -** 7 pt			
Reason : Text change as per costumer requirement accordigly arwork size revised.					
Path : M:\Govandi\Artwork\Venaa - Final Artworks in CDR\Current 08.2010\Formulation\Export\Malaysia					
NOTE TO THE PRINTER: Processor / Printer shall not make any correction / changes / deviation in the approved artwork. If any discrepancy observed in the artwork, Printer / Processor shall return the artwork to USV.					

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Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular blockade. Even if recovery from neuromuscular blockade is complete, other medicinal products used in the peri- and postoperative period could depress respiratory function and therefore ventilatory support might still be required.
Should neuromuscular blockade reoccur following extubation, adequate ventilation should be provided.

Effect on hemostasis
In a study in volunteers, doses of 4mg/kg and 16mg/kg of sugammadex resulted in maximum mean prolongations of aPTT by 17 and 22% respectively and of PT (INR) by 11 and 22% respectively. These limited mean aPTT and PT (INR) prolongations were of short duration (≤ 30 minutes). Based on the clinical data-base (N=3519) there was no clinically relevant effect of sugammadex alone or in combination with anticoagulants on the incidence of peri- or post- operative bleeding complications.
In a specific study in 1184 surgical patients who were concomitantly treated with an anticoagulant, small and transient increases were observed in aPTT and PT(INR) associated with sugammadex 4 mg/kg, which did not translate into an increased bleeding risk with sugammadex compared with usual treatment.
In in vitro experiments additional aPTT and PT prolongation was noted for sugammadex in combination with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran. Considering the transient nature of the limited prolongation of aPTT and PT caused by sugammadex alone or on top of these anticoagulants, it is unlikely that sugammadex has an increased risk of bleeding. Since bleeding risk has not been studied systematically at higher doses than sugammadex 4 mg/kg, coagulation parameters should be carefully monitored according to routine clinical practice in patients with known coagulopathies and in patients using anticoagulants who receive a dose of 16 mg/kg sugammadex.

Recurrence of neuromuscular blockade:
In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labeled for the depth of neuromuscular blockade (N=2022), an incidence of 0.20% was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence. The use of lower than recommended doses may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended.

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

Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg sugammadex)

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

When rocuronium 1.2 mg/kg is administered within 30 minutes after reversal with sugammadex, the onset of neuromuscular blockade may be delayed up to approximately 4 minutes and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes.
Based on PK modeling the recommended waiting time in patients with mild or moderate renal impairment for re-use of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after routine reversal with sugammadex should be 24 hours. If a shorter waiting time is required, the rocuronium dose for a new neuromuscular blockade should be 1.2 mg/kg.
Re-administration of rocuronium or vecuronium after immediate reversal (16 mg/kg sugammadex):
For the very rare cases where this might be required, a waiting time of 24 hours is suggested. If neuromuscular blockade is required before the recommended waiting time has passed, a nonsteroidal neuromuscular blocking agent should be used. The onset of a depolarizing neuromuscular blocking agent might be slower than expected, because a substantial fraction of postjunctional nicotinic receptors can still be occupied by the neuromuscular blocking agent.

Renal impairment:
Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis.
Interactions due to the lasting effect of rocuronium or vecuronium:
When medicinal products which potentiate neuromuscular blockade are used in the post-operative period special attention should be paid to the possibility of recurrence of neuromuscular blockade. Please refer to the package leaflet of rocuronium or vecuronium for a list of the specific medicinal products which potentiate neuromuscular blockade. In case recurrence of neuromuscular blockade is observed, the patient may require mechanical ventilation and re-administration of sugammadex

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, 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). As a result recurrence of neuromuscular blockade might be observed. In this situation the patient must be ventilated. Administration of the medicinal product which caused displacement should be stopped in case of an infusion. In situations when potential displacement interactions can be anticipated, patients should be carefully monitored for signs of recurrence of neuromuscular blockade (approximately up to 15 minutes) after parenteral administration of another medicinal product occurring within a period of 7.5 hours after sugammadex administration.

Light anesthesia:
When neuromuscular blockade was reversed intentionally in the middle of anesthesia in clinical trials, signs of light anesthesia were noted occasionally (movement, coughing, grimacing and suckling of the tracheal tube).
If neuromuscular blockade is reversed, while anesthesia is continued, additional doses of anesthetic and/or opioid should be given as clinically indicated.

Marked bradycardia:
In rare instances, marked bradycardia has been observed within minutes after the administration of sugammadex for reversal of neuromuscular blockade. Isolated cases of bradycardia with cardiac arrest have been reported. Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anti- cholinergic agents such as atropine should be administered if clinically significant bradycardia is observed.

Hepatic impairment:
Sugammadex is not metabolized nor excreted by the liver; therefore dedicated studies in patients with hepatic impairment have not been conducted. Patients with severe hepatic impairment should be treated with great caution. In case hepatic impairment is accompanied by coagulopathy see the information on the effect on hemostasis.

Use in Intensive Care Unit (ICU):
Sugammadex has not been investigated in patients receiving rocuronium or vecuronium in the ICU setting.

Use for reversal of neuromuscular blocking agents other than rocuronium or vecuronium:
Sugammadex should not be used to reverse block induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.
Sugammadex should not be used for reversal of neuromuscular blockade induced by steroidal neuromuscular blocking agents other than rocuronium or vecuronium, since there are no efficacy and safety data for these situations. Limited data are available for reversal of pancuronium induced blockade, but it is advised not to use sugammadex in this situation.

Delayed recovery:
Conditions associated with prolonged circulation time such as cardiovascular disease, old age 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.

Patients on a controlled sodium diet:
Each ml solution contains 9.19 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.

ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of sugammadex has been evaluated in 3519 unique subjects across the Pooled Phase I-III safety database. In the subject of Pooled Placebo-controlled trials where subjects received anesthesia and/or neuromuscular blocking agents (1078 subject exposures to sugammadex versus 544 to placebo), the following adverse events occurred in ≥2% of subjects treated with sugammadex and at least twice as often compared to placebo:

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

System Organ class	Adverse Reaction (Preferred Term)	Sugammadex (N=1078) %	Placebo (N=544) %
Injury, poisoning and procedural complications	Airway complication of anesthesia	4	0
	Anesthetic complication	3	<1
	Procedural hypotension	3	2
	Procedural complication	2	1
Respiratory, thoracic and mediastinal disorders	Cough	5	2

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

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

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

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

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

Description of selected adverse reactions
Drug hypersensitivity reactions:
Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers. (for information on volunteers, see Information on healthy volunteers below). In clinical trials of surgical patients, these reactions were reported uncommonly and for post- marketing reports the frequency is unknown.

These reactions varied from isolated skin reactions to serious systemic reactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to sugammadex.
Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal.

Information on healthy volunteers
A randomized, double-blind study examined the incidence of 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 after placebo or sugammadex 4 mg/kg.

There was a single case of adjudicated anaphylaxis after the first dose of sugammadex 16 mg/kg (incidence 0.7%). There was no evidence of increased frequency or severity of hypersensitivity with repeat dosing of sugammadex.

In a previous study of similar design, there were three adjudicated cases of anaphylaxis, all after sugammadex 16 mg/kg (incidence 2.0%).
The most common adverse reaction in pooled healthy volunteers was dysgeusia (10%).

Marked bradycardia:
In post-marketing, isolated cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex.

Additional information on special populations
Pulmonary patients:
In post-marketing data and in one dedicated clinical trial in patients with a history of pulmonary complications bronchospasm was reported as a possibly related adverse event. As with all patients with a history of pulmonary complications the physician should be aware of the possible occurrence of bronchospasm.

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

Birth to <2 years of age
The safety of sugammadex has been assessed in a randomized, double-blinded, active comparator controlled study of pediatric patients from birth to <2 years of age, with 107 receiving treatment with sugammadex. Adverse events occurring in ≥5% of pediatric patients are presented in the Table below. The safety profile was generally consistent with that observed in pediatric patients from 2 to <17 years of age and adults.

Pediatric Participants (Birth to <2 Years) with Specific Adverse Events Incidence ≥ 5% in One or More Treatment Groups Up to 7 Days Post-Treatment

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg	
	n	(%)	n	(%)
Participants in population	44		63	
with one or more specific adverse events	30	(68.2)	43	(68.3)
with no specific adverse events	14	(31.8)	20	(31.7)
Cardiac disorders	**3**	**(6.8)**	**0**	**(0.0)**
Gastrointestinal disorders	**6**	**(13.6)**	**4**	**(6.3)**
Vomiting	4	(9.1)	1	(1.6)
General disorders and administration site conditions	**5**	**(11.4)**	**6**	**(9.5)**
Pyrexia	3	(6.8)	3	(4.8)
Infections and infestations	**3**	**(6.8)**	**0**	**(0.0)**
Injury, poisoning and procedural complications	**19**	**(43.2)**	**35**	**(55.6)**
Procedural pain	18	(40.9)	34	(54.0)
Procedural vomiting	3	(6.8)	1	(1.6)
Metabolism and nutrition disorders	**3**	**(6.8)**	**2**	**(3.2)**
Respiratory, thoracic and mediastinal disorders	**5**	**(11.4)**	**3**	**(4.8)**

Every participant is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears in this table only if its incidence in one or more of the columns meets the incidence criterion in the table title, after rounding.

Morbidly obese patients
In one dedicated clinical trial in morbidly obese patients, the adverse reaction profile was generally similar to the profile in adult patients in pooled Phase 1 to 3 studies

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

PREGNANCY AND LACTATION

Pregnancy:
For sugammadex no clinical data on exposed pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development.
Caution should be exercised when administering sugammadex to pregnant women.

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

DRUG INTERACTIONS

The information in this section is based on binding affinity between sugammadex and other medicinal products, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking agents and the pharmacokinetic interaction between neuromuscular blocking agents and sugammadex. Based on these data, no clinically significant pharmacodynamic interaction with other medicinal products is expected, with exception of the following:
For toremifene and fusidic acid displacement interactions could not be excluded (no clinically relevant capturing interactions are expected).
For hormonal contraceptives a clinically relevant capturing interaction could not be excluded (no displacement interactions are expected).

Interactions potentially affecting the efficacy of sugammadex:
Toremifene:
For toremifene, which has a relatively high binding affinity for sugammadex and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with sugammadex could occur. The recovery of the T_4/T_1 ratio to 0.9 could therefore be delayed in patients who have received toremifene on the same day of the operation.

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

Interactions potentially affecting the efficacy of other medicinal products:
Hormonal contraceptives:
The interaction between 4 mg/kg sugammadex and a progestogen was predicted to lead to a decrease in progestogen exposure (34 % of AUC) similar to the decrease seen when a daily dose of an oral contraceptive is taken 12 hours too late, which might lead to a reduction in effectiveness. For estrogens, the effect is expected to be lower. Therefore the administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral contraceptive steroids (either combined or progestogen only). If sugammadex is administered at the same day as an oral contraceptive is taken reference is made to missed dose advice in the package leaflet of the oral contraceptive. In the case of non-oral hormonal contraceptives, the patient must use an additional non hormonal contraceptive method for the next 7 days and refer to the advice in the package leaflet of the product.

Interference with laboratory tests:
In general sugammadex does not interfere with laboratory tests, with the possible exception of the serum progesterone assay. Interference with this test is observed at sugammadex plasma concentrations of 100µg/ml.

Pediatric population
No formal interaction studies have been performed. The above mentioned interactions for adults and the warnings mentioned in the section warnings and precautions should also be taken into account for the pediatric population

OVERDOSAGE

In clinical studies, 1 case of an accidental overdose with 40 mg/kg was reported without any significant undesirable effects. In a human tolerance study sugammadex was administered in doses up to 96 mg/kg. No dose related adverse events nor serious adverse events were reported.
Sugammadex can be removed using hemodialysis with a high-flux filter, but not with a low-flux filter. Based upon clinical studies, sugammadex concentrations in plasma are reduced with a high-flux filter by about 70% after a 3 to 6-hour dialysis session.

INSTRUCTIONS OF USE

sugammadex Injection can be injected into the intravenous line of a running infusion with the following intravenous solutions: 0.9% Sodium chloride Injection, 5% Dextrose Injection, 5% Dextrose in 0.9% Sodium chloride Injection, Isolyte P with 5 % Dextrose (Arolyte P with 5 % Dextrose is used alternatively, due to unavailability of Isolyte P with 5 % dextorse, for data generation), Ringer's lactate solution and Ringer's solution. The infusion line should be adequately flushed (e.g., with 0.9% sodium chloride) between administration of sugammadex Injection and other drugs. For pediatric patients sugammadex Injection can be diluted using sodium chloride 9 mg/ml (0.9 %) to a concentration of 10 mg/ml. Any unused product or waste material should be disposed of in accordance with local requirements.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Sugammadex Injection has no known influence on the ability to drive and use machines.

PRESENTATION
Each ml contains
100 mg Sugammadex equivalent to 108.8 mg Sugammadex sodium.

PACKING:
2 mL of solution in glass vial closed with rubber stoppers with aluminium flip off seal.

STORAGE:
Store at or below 30°C. Do not freeze.
Store in the original package in order to protect from light. The vials may be stored outside the carton for up to 5 days.
For storage conditions of the diluted medicinal product, see shelf life section.

SHELF LIFE: 24 months

The sterility condition at the time of dilution would determine which shelf life would be applicable for the diluted product. From a microbiological point of view, the diluted product should be used immediately.
If the dilution is done under aseptic conditions, the shelf life of the diluted product is up to 48 hours at 2°C to 25°C. If the dilution is not performed under controlled and aseptic conditions, the shelf life of the diluted product is the responsibility of the user and would normally not be more than 24 hours at 2°C to 8°C.

Product registration holder address:
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No. 53, Jalan Tembaga SD 5/2B, Bandar Sri Damansara,
52200 Kuala Lumpur, Malaysia.

Manufacturer:
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