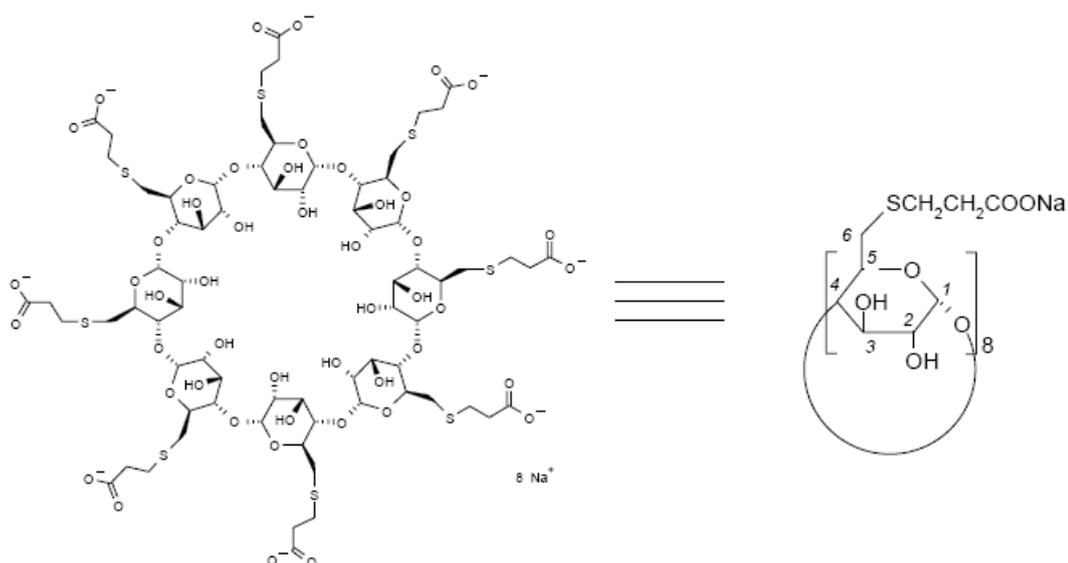


# BRIDION<sup>®</sup>

sugammadex (as sodium salt)

## (i) NAME OF THE MEDICINE

**Bridion 100 mg/mL** Solution for Injection



*Molecular Formula:* C<sub>72</sub>H<sub>104</sub>O<sub>48</sub>S<sub>8</sub>Na<sub>8</sub>

*Molecular mass:* 2178.01

*Cas. Registry No:* 343306-79-6

*Chemical Name:* octakis(6-S-(2-carboxyethyl)-6-thio)cyclomaltooctaose octasodium salt

## (ii) DESCRIPTION

Sugammadex is a white to off-white powder. It is soluble at room temperature in water, normal saline and 5% mannitol in water.

Bridion solution for injection contains sugammadex 100 mg/mL, hydrochloric acid and sodium hydrochloride for pH adjustment and Water for Injections. It is a clear and colourless to slightly yellow solution in 2 mL or 5 mL vials. The pH is between 7 and 8 and osmolality is between 300 and 500 mOsm/kg.

## (iii) PHARMACOLOGY

### 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 (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.

#### **Pharmacokinetics**

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 with sugammadex.

#### 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 function is presented in Table 1.

Table 1 Pharmacokinetic Parameters of Sugammadex Based on Population Pharmacokinetic Modeling in Children to Elderly by Renal Function

Selected patient characteristics				Mean predicted PK parameters (CV*%)		
Demo-graphics	Renal function Creatinine clearance (mL/min)			Clearance (mL/min)	Volume of distribution at steady state (L)	Elimination half- life (hr)
Adult	Normal		100	88 (22)	12	2 (22)
40 yrs 75 kg	Impaired	Mild	50	51 (22)	13	4 (22)
		Moderate	30	31 (23)	14	6 (23)
		Severe	10	9 (22)	14	19 (24)
Elderly	Normal		80	75 (23)	12	2 (21)
75 yrs 75 kg	Impaired	Mild	50	51 (24)	13	3 (22)
		Moderate	30	31 (23)	14	6 (23)
		Severe	10	9 (22)	14	19 (23)
Adolescent	Normal		95	77 (23)	9	2 (22)
15 yrs 56 kg	Impaired	Mild	48	44 (23)	10	3 (22)
		Moderate	29	27 (22)	10	5 (23)
		Severe	10	8 (21)	11	17 (23)
Child	Normal		51	37 (22)	4	2 (20)
7 yrs 23 kg	Impaired	Mild	26	19 (22)	4	3 (22)
		Moderate	15	11 (22)	4	5 (22)
		Severe	5	3 (22)	5	20 (25)

\*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: Clearance (CL) was 9% lower and volume of distribution ( $V_{ss}$ ) was 12% lower in the Japanese compared to the Caucasian subjects, but after body weight normalisation these parameters were similar in both ethnic groups. Limited data does not indicate differences in pharmacokinetic parameters in Black or African Americans.

### Body weight

Although no clinical trials have examined the pharmacokinetics of sugammadex in obese and normal individuals, population pharmacokinetic analysis of adult and elderly patients showed no clinically relevant relationship of clearance and volume of distribution with body weight.

## (iv) CLINICAL TRIALS

Sugammadex can be administered at several time points after administration of rocuronium or vecuronium bromide.

### Routine reversal

The ability of sugammadex to routinely reverse shallow or profound neuromuscular blockade induced by rocuronium or vecuronium was studied in three multicentre trials in adults.

#### **1. Comparative study of sugammadex versus neostigmine as a reversal agent of neuromuscular blockade induced and maintained by rocuronium or vecuronium, at 1-2 PTCs:**

In a multicentre, randomised, parallel group, comparative, active controlled, safety assessor blinded study comparing sugammadex and neostigmine, 157 patients (86 females and 71 males, the majority were Caucasian and ASA class 2 and 3, the median age in the rocuronium and vecuronium groups were 54 and 56 years, respectively) who were scheduled for a surgical procedure under general anaesthesia (induction with propofol, maintenance with sevoflurane) with the use of a neuromuscular blocker for endotracheal intubation and maintenance of neuromuscular blockade, 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 microgram/kg neostigmine was administered in a randomised order as single bolus injections. The time from start of administration of sugammadex or neostigmine to recovery of the  $T_4/T_1$  ratio to 0.9 was assessed. See Table 2.

The geometric mean times to recovery of the  $T_4/T_1$  ratio to 0.9 after rocuronium- or vecuronium-induced neuromuscular blockade were 17.3 times and 14.9 times faster, respectively, following the administration of sugammadex, compared with neostigmine.

Table 2: Time (min:sec) from administration of sugammadex or neostigmine at profound 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 (4.0 mg/kg)	Neostigmine (70 microgram/kg)
Rocuronium		
n	37	37
Geometric mean (95% CI)	2:52 (2:27, 3:22)	50:22 (43:29, 58:21)
Median	2:42	49:00
Range	1:13-16:05	13:16-145:40
p-value <sup>a</sup>	< 0.001	
Vecuronium		
n	47	36
Geometric mean (95% CI)	4:28 (3:20, 6:00)	66:12 (53:35, 78:51)
Median	3:15	49:53
Range	1:26-68:25	46:01-312:39
p-value <sup>a</sup>	< 0.001	

<sup>a</sup> p-value obtained from a 2-way ANOVA on log transformed times to recovery of the  $T_4/T_1$  ratio to 0.9

#### **2. Comparative study of sugammadex versus neostigmine as a reversal agent of neuromuscular blockade induced by rocuronium or vecuronium, at reappearance of $T_2$ :**

In a multicentre, randomised, parallel group, comparative, active controlled, safety assessor blinded study comparing sugammadex and neostigmine, 189 patients (87 females and 102 males, the majority were Caucasian and ASA class 1 and 2, the median age in the rocuronium and vecuronium groups were 50

and 51 years, respectively) who were scheduled for a surgical procedure with general anaesthesia (with sevoflurane) with the use of a neuromuscular blocker for endotracheal intubation and maintenance of neuromuscular blockade, 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 microgram/kg neostigmine was administered in a randomised order as single bolus injections. The time from start of administration of sugammadex or neostigmine to recovery of the  $T_4/T_1$  ratio to 0.9 was assessed. See Table 3.

The geometric mean times to recovery of the  $T_4/T_1$  ratio to 0.9 after rocuronium- or vecuronium-induced neuromuscular blockade were 12.7 times and 6.7 times faster, respectively, following the administration of sugammadex, compared with neostigmine.

Table 3: Time (min:sec) 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 (2.0 mg/kg)	Neostigmine (50 microgram/kg)
Rocuronium		
n	48	48
Geometric mean (95% CI)	1:29 (1:20, 1:39)	18:30 (14:20, 23:51)
Median	1:24	17:36
Range	0:55-5:25	3:40-106:53
p-value <sup>a</sup>	< 0.001	
Vecuronium		
n	48	45
Geometric mean (95% CI)	2:48 (2:16, 3:27)	16:48 (12:53, 21:54)
Median	2:08	18:56
Range	1:12-64:12	2:55-76:09
p-value <sup>a</sup>	< 0.001	

<sup>a</sup> p-value obtained from a 2-way ANOVA on log transformed times to recovery of the  $T_4/T_1$  ratio to 0.9

**3. Comparative study of rocuronium and sugammadex versus cisatracurium and neostigmine when neuromuscular blockade is reversed at reappearance of  $T_2$ :** In a multicentre, randomised, parallel group, comparative, active controlled, safety assessor blinded study comparing rocuronium and sugammadex versus cisatracurium and neostigmine, 73 patients (36 females and 37 males, the majority were Caucasian and ASA class 1 and 2, the median age was 43 years) who were scheduled for a surgical procedure under general anaesthesia (with propofol) with the use of a neuromuscular blocker for endotracheal intubation and maintenance of neuromuscular blockade, were randomised to rocuronium followed by 2 mg/kg sugammadex or cisatracurium followed by 50 microgram/kg neostigmine. The reversal agents were administered as single bolus injections at the reappearance of  $T_2$ . The time from start of administration of sugammadex or neostigmine to recovery of the  $T_4/T_1$  ratio to 0.9 was assessed. See Table 4.

The geometric mean time to recovery of the  $T_4/T_1$  ratio to 0.9 following reversal of rocuronium-induced neuromuscular blockade by sugammadex was 4.3 times faster than the geometric mean time to recovery of the  $T_4/T_1$  ratio to 0.9 following reversal of cisatracurium-induced neuromuscular blockade by neostigmine.

Table 4: Time (min:sec) from administration of sugammadex or neostigmine at reappearance of T<sub>2</sub> after rocuronium or cisatracurium to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9.

	Treatment regimen	
	Rocuronium and Sugammadex (2.0 mg/kg)	Cisatracurium and Neostigmine (50 microgram/kg)
n	34	39
Geometric mean (95% CI)	2:02 (1:42, 2:55)	8:46 (7:24, 10:24)
Median	1:55	7:12
Range	0:41-6:24	4:12-28:14
p-value <sup>a</sup>	< 0.001	

<sup>a</sup> p-value obtained from a 2-way ANOVA on log transformed times to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9

### Immediate reversal

A multicentre, randomised, parallel group, comparative, active controlled, safety assessor blinded study in 110 adult patients (64 females and 46 males, the majority were Caucasian and ASA class 1 and 2, the median age was 43 years scheduled for a surgical procedure with general anaesthesia with propofol) was conducted to assess the time to recovery from neuromuscular blockade induced by suxamethonium compared with recovery from neuromuscular blockade induced by rocuronium followed 3 minutes later with sugammadex. Recovery to T<sub>1</sub> of 10% after neuromuscular blockade induced by 1.2 mg/kg rocuronium reversed at 3 minutes by 16 mg/kg sugammadex was compared to spontaneous recovery after a neuromuscular blockade induced by 1 mg/kg suxamethonium. See Table 5.

The mean time to a T<sub>1</sub> of 10% (relative to the time of administration of rocuronium or suxamethonium) was approximately 2.7 minutes faster in the rocuronium + sugammadex group compared with suxamethonium alone.

Table 5: Time (min:sec) from administration of rocuronium or suxamethonium to recovery of T<sub>1</sub> 10%.

	Treatment regimen	
	Rocuronium and Sugammadex (16.0 mg/kg)	Suxamethonium (1.0 mg/kg)
n	55	55
Mean (SD)	4:22 (0:44)	7:04 (1:34)
Median (min:sec)	4:11	7:06
Range	3:28-7:43	3:45-10:28
p-value <sup>a</sup>	< 0.001	

<sup>a</sup> p-value obtained from a 2-way ANOVA on log transformed times to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9

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

Table 6: Time (min:sec) from administration of sugammadex at 3 minutes after rocuronium to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9, 0.8 or 0.7.

	T <sub>4</sub> /T <sub>1</sub> to 0.9	T <sub>4</sub> /T <sub>1</sub> to 0.8	T <sub>4</sub> /T <sub>1</sub> to 0.7
n	65	65	65
Median (min:sec)	1:31	1:09	1:08
Range	0:29-14:18	0:29-6:14	0:29-3:15

### Renal Impairment

Two open labelled 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 post-tetanic counts (PTC) (4 mg/kg, N=68). In the other study, sugammadex was administered at the reappearance of T2 (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.

#### **Safety**

Sugammadex was used safely in patients with pulmonary or cardiac complications.

### **(v) INDICATIONS**

Reversal of neuromuscular blockade induced by rocuronium or vecuronium.

### **(vi) CONTRAINDICATIONS**

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

### **(vii) PRECAUTIONS**

In volunteers, sugammadex has been administered repeatedly in 2 to up to 3 dosing periods. However, there is no experience with sugammadex on repeated exposure in patients.

#### **Immediate reversal**

There are no data for immediate reversal following vecuronium blockade (see **DOSAGE AND 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 labeled 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 **DOSAGE AND METHOD OF ADMINISTRATION** and **ADVERSE 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 ( $\leq$  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.

### **Renal impairment**

Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis (see **CLINICAL TRIALS**).

### **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**).

### **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 blockade is observed, it is advised to ventilate the patient.

### **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 **ADVERSE 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 **ADVERSE 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 benzyliisoquinolinium 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 **DOSAGE AND 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 hypersensitivity reactions appears to be dose-dependent (see **CLINICAL TRIALS** and **ADVERSE EFFECTS**).

### **Use in children**

- Bridion should not be given to children aged less than 2 years.
- Limited safety and efficacy data support use of Bridion in children aged from 2 years for routine reversal at doses to 4 mg/kg.
- Efficacy and safety of Bridion for immediate reversal in children have not been assessed.

### **Use in pregnancy** (Category B2)

There are no clinical data for exposed pregnancies. In animal studies with administration over the whole period of organogenesis, sugammadex did not affect fetal 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 fetal 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 fetus.

### **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.

### **Nonclinical toxicity**

In rat studies sugammadex showed an affinity for and persistence in bones and to a lesser extent teeth, which may reflect binding to hydroxyapatite. Bone changes suggestive of slight resorption were seen after single administration of a high dose (2000 mg/kg) in adult rats, which resulted in a drug exposure (AUC) that was 90-fold that in humans with the 4 mg/kg dose. Disruption of the enamel epithelium and abnormal white incisor discolouration were observed after daily dosing of juvenile rats for 4 weeks, but there was a high safety margin based on estimates of incisor concentrations. The clinical significance of these findings is unknown.

### **Genotoxicity**

Sugammadex was not genotoxic in *in vitro* tests for bacterial reverse mutation and chromosomal aberrations in human lymphocytes, and in *in vivo* micronucleus tests for clastogenicity.

### **Carcinogenicity**

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

### **Impairment of 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.

### **Effect on ability to drive and use machines**

The usual precautionary measures after a general anaesthetic should be taken for ambulatory patients.

### **Effect 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.

## (viii) INTERACTIONS WITH OTHER MEDICINES

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.

*Paediatric Population:* No formal interaction studies have been performed. The interactions for adults and the warnings in **PRECAUTIONS** should also be taken into account for the paediatric population.

### 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 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  $T_4/T_1$  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 or vecuronium 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 a lowering 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 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). Refer to the missed dose advice in the package insert of the oral 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.

#### *Re-administration with Neuromuscular Blocking Agents after Reversal with Sugammadex*

When rocuronium 1.2 mg/kg is administered within 30 minutes after reversal with Bridion, 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.

## **(ix) ADVERSE 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  $\geq 2\%$  of subjects treated with sugammadex.

*Table 7. 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 <sup>a</sup> (N=1078)	Placebo (N=544)
SOC	PT	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 PT in that SOC that occurred in at least 2% of sugammadex subjects.

For the adverse events listed in Table 7, 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 events**

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

**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 (see **PRECAUTIONS**).

**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 ( $\geq 1/1000$  to  $< 1/100$ ) 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 randomised, 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 (see **PRECAUTIONS**).

#### **Pulmonary patients**

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

#### **Paediatric population**

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

## **(x) DOSAGE AND ADMINISTRATION**

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.

#### **Adults**

Sugammadex can be used to reverse different levels of rocuronium or vecuronium-induced neuromuscular blockade:

##### 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 **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 **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 **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 **CLINICAL TRIALS**).

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

## Paediatric population

### Children and adolescents

For **routine** reversal of rocuronium- induced blockade at reappearance of T<sub>2</sub> in children and adolescents (2 – 17 years) 2mg/kg sugammadex is recommended. Other routine reversal situations have not been investigated and are therefore not recommended until further data become available.

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

Bridion may be diluted to increase the accuracy of dosing in the paediatric population (see **Method of Administration**).

### 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 **PRECAUTIONS** for waiting times.

Sugammadex is not recommended for use in patients with severe renal impairment (including patients requiring dialyses) (see **PRECAUTIONS**). Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of sugammadex in these patients (see **CLINICAL TRIALS**).

### Hepatic impairment

The dose recommendations are the same as for adults without hepatic impairment, as sugammadex is mainly excreted renally. See **PRECAUTIONS** for use of sugammadex when hepatic impairment is accompanied by coagulopathy.

### Elderly patients

After administration of sugammadex at reappearance of T<sub>2</sub> following a rocuronium-induced blockade, the median time to recovery of the T<sub>4</sub>/T<sub>1</sub> 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 ( $\geq$  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 **PRECAUTIONS**).

### Obese patients

In 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

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

For *paediatric patients*, Bridion can be diluted using 0.9% sodium chloride to a concentration of 25 mg/mL (see **Storage and Shelf Life**).

**Incompatibilities:** Bridion must not be mixed with other medical products except those mentioned in the above “Compatibility” section. The infusion line should be adequately flushed (e.g., with 0.9% sodium chloride) between administration of Bridion and other drugs.

Physical incompatibility was observed with verapamil, ondansetron and ranitidine.

**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 8):

Table 8: 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

When rocuronium is re-administered after sugammadex onset and duration times may be affected (see **INTERACTIONS WITH OTHER MEDICINES**).

Based on PK modelling the recommended waiting time in patients with mild or moderate renal impairment for re-use of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after routine reversal with sugammadex should be 24 hours. If a shorter waiting time is required, the rocuronium dose for a new neuromuscular blockade should be 1.2 mg/kg.

Re-administration of rocuronium or vecuronium after immediate reversal (16 mg/kg sugammadex): For the very rare cases where this might be required, a waiting time of 24 hours is suggested.

If neuromuscular blockade is required before the recommended waiting time has passed, a **nonsteroidal neuromuscular blocking agent** should be used. The onset of a depolarizing neuromuscular blocking agent might be slower than expected, because a substantial fraction of postjunctional nicotinic receptors can still be occupied by the neuromuscular blocking agent.

## (xi) OVERDOSAGE

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. For information on haemodialysis see **PRECAUTIONS**.

## (xii) PRESENTATION AND STORAGE CONDITIONS

*Bridion 100 mg/ 1mL:* Single-use injection vial of hydrolytic resistant glass closed with a grey chlorobutyl rubber closure. The rubber closure is held in position on the glass vial by a roll-on aluminium crimp-cap with a “flip-off” seal. The rubber stopper in the vial does not contain latex.

Pack size: 2 mL (10 vials) or 5 mL (10 vials)

### **Storage and shelf-life**

Store below 30°C. Do not freeze. Protect from light. Bridion has a 3-year shelf-life when stored under these conditions. When not protected from light, the vial should be used within 5 days.

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

After dilution with infusion fluids (see **DOSAGE AND ADMINISTRATION**), chemical and physical in-use stability has been demonstrated for 48 hours at 2 – 25°C. From a microbiological view point, the diluted product should be used immediately.

**(xiii) NAME AND ADDRESS OF THE SPONSOR**

Merck Sharp & Dohme (Australia) Pty Limited  
Level 1, Building A, 26 Talavera Road  
Macquarie Park, NSW 2113  
Australia

Merck Sharp & Dohme (New Zealand) Ltd  
PO Box 99851  
Newmarket  
Auckland 1149  
New Zealand

**(xiv) POISON SCHEDULE OF THE MEDICINE**

Schedule 4  
Prescription Only Medicine

**(xv) DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 28 November 2008

**(xvi) DATE OF MOST RECENT AMENDMENT:** 3 February 2016