

# NEW ZEALAND DATA SHEET

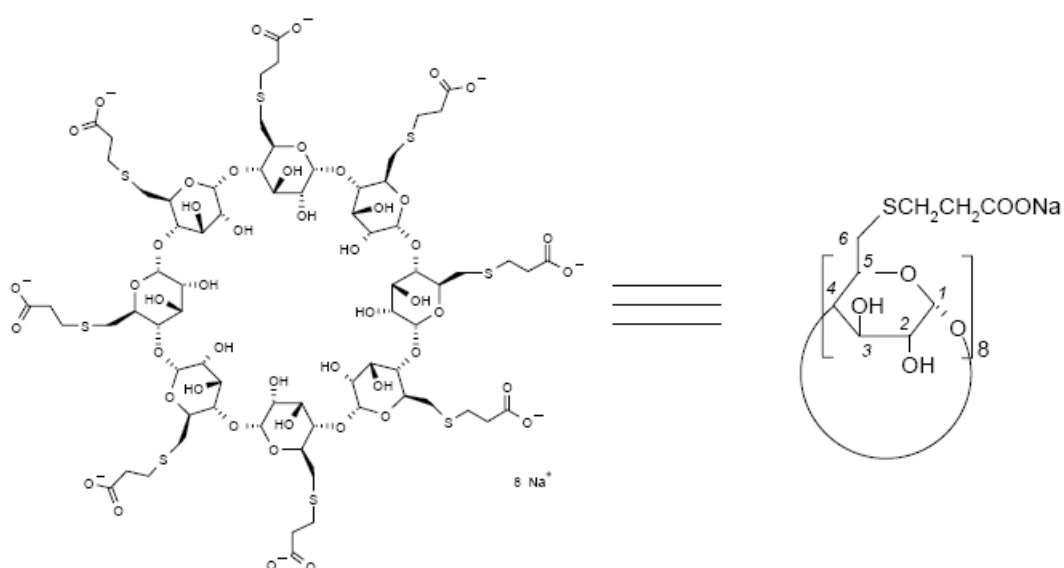
## BRIDION<sup>®</sup>

*sugammadex (as sodium salt)*

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### (i) NAME OF THE DRUG

**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**

Following intravenous administration to adult patients, sugammadex exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ( $t_{1/2}$ ) of 2.9 minutes; a slow distribution phase with a distribution half-life ( $t_{1/2}$ ) of 27 minutes; an elimination half-life of 2.2 hours and a steady state volume of distribution ( $V_{ss}$ ) of 15 litres. Clearance is estimated to be 91 mL/min. Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose.

### *Distribution*

The steady-state volume of distribution of sugammadex is 15 litres. 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.

### *Metabolism*

In 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 is 2.2 hours and plasma clearance is estimated to be 91 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

#### *Elderly and renal impairment*

Pharmacokinetic parameters in elderly patients with varying degrees of renal function, quantified by creatinine clearance (CrCL), were estimated using population pharmacokinetic (PK) analysis. A study with 51 patients of 65 to 91 years of age and CrCL varying between 26 and 144 mL/min was included in the dataset. The clearance in elderly is dependent on CrCL according to the equation:  $CL = 87 \text{ mL/min} + 0.61 \times (\text{CrCL} - 105.4)$ . The calculated PK parameters in typical elderly patients are presented in Table 1.

*Table 1: Estimates of PK Parameters of sugammadex in elderly (renal impaired) patients (75 kg bodyweight)*

PK Parameter	Normal CrCL: 80 mL/min	Mild renal impairment CrCL: 50 mL/min	Moderate renal impairment CrCL: 30 mL/min
Elimination Half-Life (h)	3.1	4.0	5.0
Volume of Distribution at Steady State (L)	16	16	16
Clearance (mL/min)	72	54	41

### Paediatrics

Pharmacokinetics in paediatric patients (n=51) with ages ranging from 0 to 17 years were evaluated using population pharmacokinetics (PK) analysis. In patients under age 18, volume of distribution and clearance increase with age according to the equations:  $CL = 91 \text{ mL/min} \times e^{(-0.0808 \times (18 - \text{age}))}$  and  $V_{ss} = 14.6L \times e^{(-0.156 \times (18 - \text{age}))}$ . The PK parameters of two typical paediatric patients are summarised in Table 2.

*Table 2: PK Parameters of sugammadex in typical paediatric patients*

PK Parameter	Child (Age: 8yr)	Adolescent (Age: 15yr)
Elimination Half-Life (h)	0.9	1.7
Volume of Distribution at Steady State (L)	3.1	9.1
Clearance (mL/min)	41	71

### 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.

### 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 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 17.3 times and 14.9 times faster, respectively, following the administration of sugammadex, compared with neostigmine.

Table 3: 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 4.

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 4: 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 5.

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 5: Time (min:sec) from administration of sugammadex or neostigmine at reappearance of  $T_2$  after rocuronium or cisatracurium to recovery of the  $T_4/T_1$  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  $T_4/T_1$  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  $T_1$  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 6.

The mean time to a  $T_1$  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 6: Time (min:sec) from administration of rocuronium or suxamethonium to recovery of  $T_1$  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  $T_4/T_1$  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 7: Time (min:sec) 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 (min:sec)	1:31	1:09	1:08
Range	0:29-14:18	0:29-6:14	0:29-3:15

### 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.

### **Neuromuscular blockade prolonged (i.e slow recovery from blockade)**

In clinical trials, a prolonged neuromuscular blockade was reported mainly when sub-optimal doses (in dose-finding studies) were administered. In order to prevent prolonged neuromuscular blockade, doses lower than the recommended doses (see **DOSAGE AND ADMINISTRATION**) should not be used.

### **Renal impairment**

In patients with severe renal failure (creatinine clearance < 30 mL/min) the excretion of sugammadex or the sugammadex-rocuronium complex was delayed; however, in these patients there were no signs of recurrence of neuromuscular blockade. Data from a limited number of renally impaired patients requiring dialysis indicate inconsistent decrease of plasma levels of sugammadex by haemodialysis. The use of sugammadex in patients with severe renal impairment is strongly discouraged.

### **Hepatic impairment**

Sugammadex is not metabolised or excreted by the liver; therefore dedicated studies in patients with hepatic impairment have not been conducted. According to a Pharmacokinetic-Pharmacodynamic (PK-PD) model simulation, the time to recovery in patients with severe hepatic impairment, under worst-case assumptions, is predicted to be slower when using the recommended dose. Refer Table 8.

*Table 8: Simulated recovery time to 90% TOF twitch height after reversal of rocuronium-induced NMB with different dose levels of sugammadex administered at different time points in patients with hepatic impairment and normal patients.*

<i>Sugammadex dose / time point of administration</i>	<i>Normal patient (minutes)</i>	<i>Severe hepatic impairment (minutes)</i>
2 mg/kg at reappearance of T <sub>2</sub> after 0.6 mg/kg rocuronium bromide	1.86	4.38
4mg/kg, 15 minutes after 0.6 mg/kg rocuronium bromide	1.76	3.43
16 mg/kg, 3 minutes after 1.2 mg/kg rocuronium bromide	1.32	1.90

### **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 REACTIONS).

### **Use in ICU**

Sugammadex has not been investigated in the ICU setting.

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

Sugammadex should not be used to reverse blockade induced by nonsteroidal neuromuscular blocking agents such as suxamethonium or benzylisoquinolinium compounds.

Sugammadex should not be used for reversal of neuromuscular blockade induced by steroidal neuromuscular blocking agents other than rocuronium or vecuronium, since there are no efficacy and safety data for these situations.

Limited data are available for reversal of pancuronium-induced blockade, but sugammadex is not recommended to reverse blockade induced with pancuronium.

### **Delayed recovery**

Conditions associated with prolonged circulation time such as cardiovascular disease, old age, or oedematous state 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 (see ADVERSE REACTIONS).

### **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.

### **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**

Long-term carcinogenicity studies with sugammadex have not been conducted.

### **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.

### **Interactions with other medicines**

No formal clinical interaction studies have been conducted in adults with sugammadex and other drugs. 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 strategy (based on binding affinity between sugammadex and other drugs, preclinical experiments and simulations of a Pharmacokinetic-Pharmacodynamic (PK – PD) model) was applied to assess both the capturing and displacement interactions. Based on *in vitro* data and taking into consideration pharmacokinetics and other relevant information, no clinically significant pharmacodynamic interaction with other drugs are expected, with the exception of toremifene, flucloxacillin and hormonal contraceptives (see below). For these drugs a clinical 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 (see also **DOSAGE AND ADMINISTRATION**)

##### *Toremifene, fusidic acid*

For toremifene and fusidic acid, which have a relatively high affinity constant and relatively high plasma concentrations, 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.

##### *Flucloxacillin*

High doses of flucloxacillin (infusion of 500 mg or more) might cause some displacement of rocuronium or vecuronium from sugammadex. The use of high doses of flucloxacillin in the pre-operative phase might give some delay in the recovery for the  $T_4/T_1$  ratio to 0.9. The use of high doses of flucloxacillin in the post-operative phase (up to 3 times the half-life of sugammadex (2.2 hours; see **Pharmacokinetics** for the half-lives in elderly, renally impaired and paediatric patients)) should be avoided. Ventilation should be closely observed in case it is essential to administer flucloxacillin.

#### Interactions potentially affecting the efficacy of other drugs (see also **DOSAGE AND ADMINISTRATION**)

##### *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 missed. Therefore the administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily

dose of **oral** contraceptive steroids. 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.

#### Potential interactions

*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) would be 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.

*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 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 blockade (approximately up to 15 minutes) after parenteral administration of another medicinal product occurring within a period of 6 hours after sugammadex administration.

#### **Effect on laboratory tests**

In general sugammadex does not interfere with laboratory tests, with the possible exception of the serum progesterone assay and some coagulation parameters [aPTT, PT and PT (INR)]. This interference was observed in plasma samples spiked with a concentration of sugammadex in the same range as obtained for  $C_{max}$  after a dose of 16 mg/kg.

In a placebo-controlled trial in healthy volunteers, sugammadex caused small increases in aPTT, PT and PT(INR) which did not reach statistical significance. The effect of sugammadex on haemostasis in patients with pre-existing coagulation abnormalities has not been examined. It is recommended that these patients have their aPTT, PT and PT(INR) monitored after administration of sugammadex.

## **(viii) ADVERSE REACTIONS**

The safety of sugammadex has been evaluated based on an integrated safety database of approximately 1700 patients and 120 volunteers. Next to this database, adverse events in the pooled phase 1-3 trials database (640 patients on sugammadex and 140 on placebo group) was also used in the evaluation of adverse events:

Table 9: Adverse events by MedDRA system organ class (SOC) and preferred term (PT) in at least 2% of sugammadex subjects in pooled Phase 1-3 trials with a placebo group

MedDRA 9.1		Rocuronium or vecuronium +	
		Sugammadex (N=640)	Placebo (N=140)
SOC	PT	n (%)	n (%)
At least one AE	Total	437 (68)	101 (72)
Injury, poisoning and procedural complications	Total	242 (38)	56 (40)
	Procedural pain	134 (21)	43 (31)
	Anaesthetic complication	52 (8)	2(1)
	Procedural hypotension	31 (5)	4 (3)
	Procedural hypertension	16 (3)	4 (3)
	Postoperative wound complication	13 (2)	3 (2)
Gastrointestinal disorders	Total	175 (27)	41 (29)
	Nausea	106 (17)	25 (18)
	Vomiting	61 (10)	11 (8)
	Constipation	15 (2)	7 (5)
	Abdominal pain	15 (2)	3 (2)
	Diarrhoea	14 (2)	4 (3)
General disorders and administration site conditions	Total	107 (17)	27 (19)
	Pain	37 (6)	7 (5)
	Pyrexia	33 (5)	11 (8)
	Chills	22 (3)	3 (2)
Investigations	Total	79 (12)	13 (9)
	Electrocardiogram QT corrected interval prolonged	15 (2)	2 (1)
	Beta 2 microglobulin urine increased <sup>a</sup>	15 (2)	4 (3)
	Albumin urine present	10 (2)	0 (0)
Respiratory, thoracic and mediastinal disorders	Total	79 (12)	14 (10)
	Pharyngolaryngeal pain	31 (5)	9 (6)
	Cough	19 (3)	2 (1)
Nervous system disorders	Total	70 (11)	22 (16)
	Headache	29 (5)	11 (8)
	Dizziness	13 (2)	4 (3)
	Hypoaesthesia	12 (2)	1 (1)
Musculoskeletal and connective tissue disorders	Total	49 (8)	9 (6)
	Back pain	20 (3)	3 (2)
Renal and urinary disorders	Total	44 (7)	10 (7)
Vascular disorders	Total	38 (6)	9 (6)
	Hypertension	14 (2)	4 (3)
	Hypotension	12 (2)	2 (1)
Psychiatric disorders	Total	30 (5)	6 (4)
	Insomnia	11 (2)	3 (2)
Skin & subcutaneous tissue disorders	Total	20 (3)	10 (7)
Metabolism and nutrition disorders	Total	21 (3)	3 (2)
Ear & labyrinth disorders	Total	17 (3)	5 (4)
	Vertigo	14 (2)	4 (3)
Cardiac disorders	Total	15 (2)	8 (6)
Infections and infestations	Total	12 (2)	6 (4)

<sup>a</sup> Includes AEs coded to beta 2 microglobulin urine increased (13 sugammadex subjects, 2 placebo subjects) plus AEs coded to beta 2 microglobulin increased (2 sugammadex subjects, 2 placebo subjects).

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.

The following adverse events showed a dose-response, or occurred in the total sugammadex group with a frequency of 2% or more and at least twice as often as compared to the placebo group.

Dysgeusia: This was reported in 12% of the volunteers in phase 1 studies (versus 4% in placebo). Dysgeusia (metallic or bitter taste) was mainly seen after doses of 32 mg/kg sugammadex or higher. It has not been reported in patients (as such it is not in Table 9).

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.

Neuromuscular blockade prolonged (i.e recurrence of blockade): In pooled phase I – III studies with a placebo group, the incidence of recurrence of blockade as measured with neuromuscular monitoring was 2% after sugammadex and 0% in the placebo group. Virtually all of these cases were from dose-finding studies in which a sub-optimal dose (less than 2 mg/kg) was administered.

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 1% of the patients and in none of the placebo group. Most occurrences of anaesthetic complications were mild to moderate.

Drug hypersensitivity reactions: Hypersensitivity reactions have occurred in some patients and volunteers. In clinical trials 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 and swelling of tongue and pharynx. Severe hypersensitivity reactions can be fatal.

**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.

## **(ix) 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

The same dose recommendations as for adults can be followed for **routine** reversal of rocuronium-induced blockade at reappearance of  $T_2$  in children and adolescents (2 – 17 years). 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**

#### Mild and moderate renal impairment (creatinine clearance between 30 and 80 mL/min)

The dose recommendations are the same as for adults. For re-administration with rocuronium or vecuronium see **PRECAUTIONS** for waiting times.

For severe renal impairment (including patients requiring dialyses) see **PRECAUTIONS**.

#### 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 ( $\geq 75$  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.

#### Hepatic impairment

The dose recommendations are the same as for adults, as sugammadex is mainly excreted renally. Recovery times might be prolonged (see **PRECAUTIONS**).

### **Method of Administration**

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

**Compatibility:** Sugammadex can be injected into the intravenous line of a running infusion with the following intravenous solutions: 0.9% sodium chloride; 5% 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. If Bridion is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g with 0.9% sodium chloride) between administration of Bridion and drugs for which incompatibility with Bridion has been demonstrated or for which compatibility with Bridion has not been established.

Physical incompatibility was observed with verapamil, ondansetron and ranitidine.

Waiting times for re-administration with neuromuscular blocking agents after reversal with sugammadex (based on a PK-PD model simulation and the half-life of sugammadex) If re-administration of rocuronium or vecuronium is required after reversal with sugammadex, the following waiting times are recommended (see Table 10):

Table 10: In patients with **normal** renal function (creatinine clearance >80 mL/min)

Previously administered dose of sugammadex	Time before re-administration (hours)		
	Re-administration dose of 0.6 mg/kg rocuronium bromide	Re-administration dose of 1.2 mg/kg rocuronium bromide	Re-administration dose of 0.1 mg/kg vecuronium bromide
2 (mg/kg)	6 hour	No waiting time	10 hour
4 (mg/kg)	8 hour	2 hour	12 hour
16 (mg/kg)	12 hour	6 hour	16 hour

In patients with:

- **mild** renal impairment (creatinine clearance between 50 and 80 mL/min) these times should be **doubled**.
- **moderate** renal impairment (creatinine clearance between 30 and 50 mL/min) these times should be **trebled**.
- for **severe** renal impairment (creatinine clearance < 30 mL/min) the use of sugammadex is strongly discouraged (see **PRECAUTIONS**)

Re-administration of 1.2 mg/kg rocuronium bromide at the recommended waiting time may be associated with a predicted median onset time (defined as time to TOF twitch height 10% of the baseline twitch height) of 1.9 minutes (2 hour after 4 mg/kg sugammadex) and 2.8 minutes (10 minutes after 2 mg/kg sugammadex). These onset times are slightly slower than predicted for the onset time of 0.6 mg/kg rocuronium bromide (1.7 minutes) without sugammadex.

If neuromuscular blockade is required before the recommended waiting time has passed, a **nonsteroidal neuromuscular blocking agent** should be used.

## **(x) 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. For information on haemodialysis see **PRECAUTIONS**.

## **(xi) PRESENTATION**

*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<sup>0</sup>C. Do not freeze. Store in the original package. Bridion has a 3-year shelf-life when stored under these conditions. The vials may be stored out of the carton for up to 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.

## **(xii) POISON SCHEDULE OF THE DRUG**

Schedule 4  
Prescription Only Medicine

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

*In Australia:*  
Schering-Plough Pty Limited  
Level 4, 66 Waterloo Road  
North Ryde NSW 2113  
AUSTRALIA

*In New Zealand:*  
Merck Sharp & Dohme (NZ) Ltd  
P O Box 99 851  
Newmarket  
Auckland 1149

Tel: 0800 500 673

**Date of Preparation:** 21 June 2011

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