

**Product name: Bridion 100 mg/ml**

**Component: English Package Insert**

**Date Approved: 11 June 2015**

## **SCHEDULING STATUS**

S4

## **PROPRIETARY NAME AND DOSAGE FORM**

BRIDION®

100 mg/ml

Solution for Injection

## **COMPOSITION**

Each ml contains 100 mg sugammadex (as the sodium salt).

2 ml contains 200 mg sugammadex (as the sodium salt).

Each ml contains 9,7 mg sodium.

**Inactive ingredients:** Water for injection, hydrochloric acid and/or sodium hydroxide.

## **PHARMACOLOGICAL CLASSIFICATION**

A.34 Other

## **PHARMACOLOGICAL ACTION**

### **Pharmacodynamic Properties**

Sugammadex sodium injection is a modified cyclodextrin. It is a selective relaxant binding agent (SRBA) which forms a complex with the neuromuscular blocking agents rocuronium and vecuronium, and it reduces the amount of neuromuscular blocking agent available to bind to

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nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium.

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.

### **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 anaesthetised subjects.

### **Distribution**

The observed steady-state volume of distribution of sugammadex sodium is approximately 11 to 14 litres in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Neither sugammadex nor rocuronium bind to plasma proteins or erythrocytes. Sugammadex sodium exhibits linear kinetics in the dose range of 1 to 16 mg/kg when administered as an IV bolus dose.

### **Metabolism**

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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 anaesthetised patients with normal renal function the elimination half-life of sugammadex sodium is about 2 hours and the estimated plasma clearance is about 84 ml/min. A mass balance study demonstrated that > 90 % of the dose was excreted within 24 hours. Ninety six percent (96 %) of the dose was excreted in urine, of which at least 95 % could be attributed to unchanged sugammadex. Excretion via faeces or expired air was < 0,02 % of the dose. Administration of sugammadex sodium 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 approximately 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. Predicted pharmacokinetic parameters of sugammadex by age group and renal function based on compartmental modelling are presented below:

<b>Selected patient characteristics</b>	<b>Predicted PK parameters</b>
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Demographics	Renal function (creatinine clearance in ml/min)		Clearance in ml/min (CV)	Volume of distribution at steady state in litres	Elimination half-life in hours (CV)
Adult 40 years 75 kg	Normal	100	84 (22 %)	11,9	2,0 (19 %)
	Impaired	50	48 (22 %)	13,1	3,6 (20 %)
		30	29 (23 %)	13,7	6,1 (21 %)
		10	9 (19 %)	14,2	20,3 (20 %)
Elderly 75 years 75 kg	Normal	80	72 (26 %)	12,4	2,4 (23 %)
	Impaired	50	49 (22 %)	13,1	3,5 (19 %)
		30	29 (22 %)	13,7	6,1 (20 %)
		10	8 (19 %)	14,2	21,0 (23 %)
Adolescent 15 years 56 kg	Normal	95	76 (20 %)	9,3	1,7 (17 %)
	Impaired	48	45 (24 %)	10,1	3,0 (21 %)
		29	26 (22 %)	10,5	5,2 (19 %)
		10	7 (18 %)	10,9	17,8 (18 %)
Child 7 years 23 kg	Normal	51	40 (21 %)	4,3	1,5 (16 %)
	Impaired	26	20 (20 %)	4,5	2,9 (19 %)
		15	11 (27 %)	4,6	5,2 (24 %)
		5	3 (22 %)	4,7	19,4 (23 %)

Mean and coefficient of variation (CV in %) are presented. For Volume of distribution, no CV could be estimated from the model.

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## INDICATIONS

BRIDION is indicated for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium. BRIDION is also indicated for the immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. For the paediatric population, BRIDION is only recommended for routine reversal of rocuronium induced blockade in children above 7 years of age.

## CONTRA-INDICATIONS

BRIDION is contra-indicated in patients with known hypersensitivity to sugammadex sodium or to any of the inactive ingredients.

## WARNINGS AND SPECIAL PRECAUTIONS

**BRIDION is not to be used to reverse depolarising neuromuscular blocking agents.**

**Waiting times for re-administration with neuromuscular blocking agents (NMBA) after reversal with BRIDION.**

Re-administration of rocuronium or vecuronium after a recommended dose reversal (up to 4 mg/kg sugammadex):

<b>Minimum waiting time</b>	<b>NMBA (e.g. Esmeron and Norcuron) and dose to be administered</b>
5 minutes	1,2 mg/kg rocuronium
4 hours	0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium

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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):

A waiting time of 24 hours is recommended.

If neuromuscular blockade is required before the recommended waiting time has passed, a **non-steroidal neuromuscular blocking agent** should be used. The onset of a depolarising neuromuscular blocking agent might be slower than expected, because a substantial fraction of post-junctional nicotinic receptors may still be occupied by the neuromuscular blocking agent.

### **Medicine Hypersensitivity**

Doctors should be prepared for the possibility of medicine hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions.

### **Renal Impairment**

BRIDION is not recommended for use in patients with severe renal impairment, creatinine clearance < 30 ml/min, including requiring dialysis (see “**PHARMACOLOGICAL ACTION, Pharmacokinetic Properties**”).

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Because of the estimated prolonged half-life of sugammadex in severe renally impaired patients, a full neuromuscular blockade may not be achieved after re-use of 0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium within 24 hours after sugammadex reversal.

### **Marked Bradycardia**

Marked bradycardia has been observed within minutes after the administration of BRIDION for reversal of neuromuscular blockade. Cases of bradycardia with cardiac arrest have been reported (see “**SIDE EFFECTS**”). Patients should be closely monitored for haemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anticholinergic agents such as atropine should be administered if clinically significant bradycardia is observed.

### **Monitoring Respiratory Function during Recovery**

Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular block. Even if recovery from neuromuscular blockade is complete, other medicines used in the peri- and post-operative period could depress respiratory function and therefore ventilatory support might still be required.

Should neuromuscular blockade re-occur following extubation, adequate ventilation should be provided.

### **Effect on Haemostasis**

In *in-vitro* experiments additional aPTT and PT prolongation was noted for BRIDION in combination with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran.

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In a study in volunteers, doses of 4 mg/kg and 16 mg/kg of BRIDION 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 ( $\leq$  30 minutes).

Based on the clinical database (n=1 738) there was no clinically relevant effect of BRIDION alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications.

Since there is no information on the use of BRIDION in patients with known coagulopathies, coagulation parameters should be carefully monitored according to routine clinical practice.

### **Delayed Recovery**

Conditions associated with prolonged circulation time such as cardiovascular disease, old age (see “**DOSAGE AND DIRECTIONS FOR USE**” for the time to recovery in elderly), or oedematous state (e.g. severe hepatic impairment) may be associated with longer recovery times.

### **Hepatic Impairment**

BRIDION is not metabolised nor excreted by the liver; therefore dedicated studies in patients with hepatic impairment have not been conducted. Hepatic impairment may be accompanied by coagulopathy (see the information on the “**Effect on Haemostasis**” above).



### **Light Anaesthesia**

When neuromuscular blockade was reversed intentionally in the middle of anaesthesia in clinical trials, signs of light anaesthesia were noted occasionally (movement, coughing, grimacing and sucking 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.

### **Use in Intensive Care Unit (ICU)**

BRIDION 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**

BRIDION should not be used to reverse block induced by non-steroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.

BRIDION should not be used for reversal of neuromuscular blockage 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 blockage, but it is advised not to use BRIDION in this situation.

### **Effects on Ability to Drive and Use Machines**

BRIDION has no known influence on the ability to drive and use machines.

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## **INTERACTIONS**

The information reported in this section is based on binding affinity between BRIDION and other medicines, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking agents and sugammadex.

Based on these data, no clinically significant pharmacodynamic interaction with other medicines are expected, with the exception of toremifene, fusidic acid and hormonal contraceptives. For these medicines, a clinically relevant interaction could not be excluded.

No clinically relevant interactions were reported during the clinical development. Due to the administration of certain medicines after sugammadex, theoretically rocuronium or vecuronium could be displaced from BRIDION. As a result recurrence of neuromuscular blockade might be observed. In this situation the patient must be ventilated.

Administration of medicines 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 re-occurrence of blockade (approximately up to 15 minutes), after parenteral administration of another medicine occurring within a period of 7,5 hours after BRIDION administration.

BRIDION should be used cautiously when co-administered with:

### **Toremifene**

For toremifene, which has a relatively high affinity constant and relatively high plasma concentrations, some displacement of vecuronium or rocuronium from the complex with BRIDION could occur.

The recovery of the train of four ratio,  $T_4/T_1$  to 0,9 could therefore be delayed in patients who have received toremifene on the same day of surgery (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

#### **Intravenous Administration of Fusidic Acid**

The use of fusidic acid in the pre-operative phase may cause some delay in the recovery of the  $T_4/T_1$  ratio to 0,9.

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 to 3 days.

#### **Hormonal Contraceptives**

In a simulation performed with a PK-PD model, it was found that the interaction between 4 mg/kg BRIDION 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.

Therefore, the administration of a bolus dose of BRIDION is considered to be equivalent to one missed daily dose of **oral** contraceptive steroids.

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Please refer to the missed dose advice in the package insert of the oral contraceptive, for any action required if an oral contraceptive is taken on the same day that BRIDION 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.**

### **Interference with Laboratory Tests**

BRIDION has been shown to interfere with the serum progesterone assay.

This interference was observed in plasma samples spiked with a concentration of BRIDION in the same range as obtained for  $C_{max}$  after a dose of 16 mg/kg.

### **Paediatric Population**

No formal interaction studies have been performed. The above-mentioned interactions for adults and the warnings should also be taken into account for the paediatric population.

## **PREGNANCY AND LACTATION**

### **Pregnancy**

**The safety in pregnant women has not been established.**

### **Lactation**

Excretion of sugammadex in human milk has not been studied, but can be expected based on the pre-clinical data.

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## **DOSAGE AND DIRECTIONS FOR USE**

BRIDION Injection should be administered under the supervision of an anaesthetist. BRIDION Injection should be administered intravenously as a single bolus injection. The bolus injection may be given rapidly, within 10 seconds, directly into a vein or into an existing IV line.

BRIDION can be injected into the intravenous line of a running infusion with the following intravenous solutions: Sodium chloride 9 mg/ml (0,9 %), glucose 50 mg/ml (5 %), sodium chloride 4,5 mg/ml (0,45 %) and glucose 25 mg/ml (2,5 %), Ringer's lactate solution, Ringer's solution, glucose 50 mg/ml (5 %) in sodium chloride 9 mg/ml (0,9 %). For paediatric patients BRIDION can be diluted using sodium chloride 9 mg/ml (0,9 %) to a concentration of 10 mg/ml.

BRIDION has only been administered as a single bolus injection in clinical trials.

The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of the neuromuscular blockade. When certain medicines that may cause displacement interactions are administered parenterally within 7,5 hours of BRIDION, patients should be monitored for signs of recurrence of neuromuscular blockade.

The recommended dose of BRIDION depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen.

BRIDION can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade.

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### **Routine Reversal of Neuromuscular Blockade**

A dose of 4 mg/kg BRIDION is recommended if recovery has reached 1 to 2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

A dose of 2 mg/kg BRIDION is only recommended if spontaneous recovery has reached the reappearance of T<sub>2</sub> (shallow blockade) following rocuronium or vecuronium induced blockade (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

### **Immediate Reversal**

If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16 mg/kg BRIDION is recommended. There is no data to recommend the use of BRIDION for immediate reversal following vecuronium induced blockade.

### **Additional Information on Special Population Groups**

#### **Renal Impairment**

For mild and moderate renal impairment (creatinine clearance  $\geq 30$  and  $< 80$  ml/min): The dose recommendations are the same as for adults without renal impairment. The use of BRIDION in patients with severe renal impairment including patients requiring dialysis (CrCl  $< 30$  ml/min) is not recommended (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of BRIDION in these patients.

### **Elderly Patients**

After administration of BRIDION 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 to 64 years) was 2,2 minutes, in elderly adults (65 to 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 (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

### **Obese Patients**

In obese patients, the dose of BRIDION 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 BRIDION 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 BRIDION in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

### **Paediatric Population**

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The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T<sub>2</sub>). There is insufficient information on the use of BRIDION for children < 7 years of age. There is no information on BRIDION use for neonates. Therefore BRIDION is not recommended for use in these populations.

### **Children and Adolescents**

For reversal of rocuronium induced blockade at reappearance of T<sub>2</sub> in children and adolescents (7 to 17 years) 2 mg/kg BRIDION is recommended.

**Immediate** reversal in children and adolescents has not been investigated and is therefore not recommended.

BRIDION 100 mg/ml may be diluted to 10 mg/ml to increase the accuracy of dosing in the paediatric population, 7 years and older.

### **SIDE EFFECTS**

The safety of BRIDION has been evaluated based on an integrated safety database of approximately 1 700 patients and 120 volunteers.

<b>Table 1: Treatment-related undesirable effects reported in the pivotal clinical study of BRIDION (MedDRA 11.1)</b>	
Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000 to < 1/100)	
<b>Immune system disorders</b>	
Uncommon	Medicine hypersensitivity reactions



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<b>Injury, poisoning and procedural complications</b>	
Uncommon	Anaesthetic complication
Common with sub-optimal doses	Prolonged neuromuscular blockade
<b>Nervous system disorders</b>	
Very common	Dysgeusia

### **Anaesthetic Complications**

Anaesthetic complications, indicative of the restoration of neuromuscular function, include movement of a limb or the body or coughing during the anaesthetic procedure or during surgery, grimacing, or sucking on the endotracheal tube, was judged to be related to treatment in about 1 % of the patients and in none of the placebo group. Most occurrences of anaesthetic complications were mild to moderate.

### **Recurrence of Neuromuscular Blockade**

In the database of pooled phase I to III studies with a placebo group, the incidence of recurrence of neuromuscular blockade as measured with neuromuscular monitoring was 2 % after BRIDION and 0 % in the placebo group. Virtually all of these cases were from dose-finding studies in which a sub-optimal dose (< 2 mg/kg) was administered. In cases where recurrence of neuromuscular blockade is observed, the patient must be ventilated.

### **Medicine Hypersensitivity Reactions**

Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers (for information on volunteers, see “**Information on healthy volunteers**” below). In

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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 BRIDION.

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

### **Information on Healthy Volunteers**

Hypersensitivity reactions, including anaphylaxis, have been observed with BRIDION. In a study in healthy conscious volunteers (placebo, n=150; 4 mg/kg, n=148; and 16 mg/kg, n=150), hypersensitivity reactions were reported commonly with BRIDION 16 mg/kg and uncommonly with BRIDION 4 mg/kg or placebo. In this study, dose dependent trends were also observed for dysgeusia, nausea and flushing.

### **Marked Bradycardia**

In post-marketing, cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

### **Additional Information on Special Populations**

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### **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.

### **Paediatric Population**

A limited database suggests that the safety profile of BRIDION (up to 4 mg/kg) in paediatric patients above 7 years old, was similar to that in adults.

### **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

BRIDION can be removed using haemodialysis with a high-flux filter, but not with a low-flux filter. Based upon clinical studies, BRIDION concentrations in plasma are reduced with a high-flux filter by about 70 % after a 3 to 6 hour dialysis session.

### **IDENTIFICATION**

BRIDION 100 mg/ml is a clear and colourless to slightly yellow solution with pH of between 7 and 8.

### **PRESENTATION**

BRIDION is packed in colourless, glass vials, sealed with grey, chlorobutyl rubber stoppers firmly sealed with aluminium crimp-cap with polypropylene, "flush edge", flip-off buttons. The rubber stoppers do not contain latex.

Pack sizes: 10 vials of 2 ml.

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### **STORAGE INSTRUCTIONS**

Store at or below 30 °C. Do not freeze. Keep the vial in the outer carton in order to protect from light. When not protected from light, the vial should be used within 5 days.

After first opening and dilution, chemical and physical in-use stability has been demonstrated for 48 hours at 2 to 25 °C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Keep out of reach of children.

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

### **REGISTRATION NUMBER**

44/34/0432

### **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

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