PRODUCT MONOGRAPH

BRIDION®

solution for injection,
100 mg/mL sugammadex (as sugammadex sodium)

Selective Relaxant Binding Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous	Solution for injection, 100 mg/mL (as sugammadex sodium)	Hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection

INDICATIONS AND CLINICAL USE

BRIDION® (sugammadex sodium) is indicated for reversal of moderate to deep neuromuscular blockade induced by rocuronium or vecuronium in adults undergoing surgery.

Pediatrics (<18 years of age):
The safety and efficacy of BRIDION® in pediatric patients have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. Hypersensitivity reactions, ranging from isolated skin reactions to serious systemic reactions (i.e. anaphylaxis, or anaphylactic reactions), have occurred in individuals with or without prior exposure to sugammadex (see WARNINGS AND PRECAUTIONS, **Serious Warnings and Precautions**, **Hypersensitivity Reactions**; ADVERSE REACTIONS, **Hypersensitivity Reactions)**.

For a complete listing of the medicinal and nonmedicinal ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- BRIDION® should be administered by trained healthcare providers familiar with the use, actions, characteristics, and complications of neuromuscular blocking agents (NMBA) and neuromuscular block reversal agents.
- BRIDION® may cause hypersensitivity reactions, including anaphylaxis or anaphylactoid reactions, on first or subsequent exposure. Clinicians should take the necessary precautions for the possibility of such reactions (see **Hypersensitivity Reactions**).

Hypersensitivity Reactions

A designated clinical trial in 375 healthy volunteers given up to 3 doses of placebo or sugammadex shows that sugammadex may cause hypersensitivity reactions, including on first exposure. The observed rates were 1.3% (1/76) on placebo, 6.6% (10/151) on 4 mg/kg, and 9.5% (14/148) on 16 mg/kg. One case of anaphylaxis was seen in the group on 16 mg/kg (0.7%, 1/148). Anaphylaxis and anaphylactoid reactions have also been reported in the post-marketing setting, including at doses in the range of 2 – 4 mg/kg.The most commonly described clinical features in reports of anaphylaxis were dermatologic symptoms (including urticaria, rash, erythema, flushing and skin eruption); and clinically important hypotension often requiring the use of vasopressors for circulatory support. In addition, prolonged hospitalization and/or the use of additional respiratory support until full recovery (re-intubation, prolonged intubation, manual or mechanical ventilation) have been noted in a number of the anaphylaxis reports.

The mechanism of the hypersensitivity reactions is not well understood. Laboratory indicators of a specific immune-mediated reaction may or may not be present.

Cardiovascular

Marked bradycardia

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

Peri-Operative Considerations

Anesthetic Complication

The depth of anesthesia should be carefully monitored and maintained whenever a neuromuscular relaxant is used, as well as when its effects are reversed. If neuromuscular blockade is reversed while anesthesia is continued, anesthetic management may need to be adjusted as clinically indicated (see ADVERSE REACTIONS).

When neuromuscular blockade was reversed in the middle of anesthesia in clinical trials, i.e. when investigating urgent reversal, signs of light anesthesia were noted occasionally (movement, coughing, grimacing and suckling of the tracheal tube).

Awareness under surgical anesthesia is a serious complication associated with excessive neuromuscular blockade without adequate analgesia and sedation. Excessive use of rocuronium or vecuronium may potentially obscure the signs of inadequate anesthesia. Its use without adequate management of the depth of anesthesia is associated with an increase frequency of this complication. Such practice should be avoided even when BRIDION® can be used to accelerate the reversal of deep neuromuscular blockade induced by rocuronium or vecuronium.

After reversal of neuromuscular blockade with BRIDION®, care must be taken to assess the recovery from the effects of the anesthetics, while observing any signs of hypersensitivity reactions. Clinical trial data indicate that the speed of emergence from anesthesia may vary considerably from patient to patient, depending on the residual effects of the anesthetics given during surgery.

Delayed Recovery
Prolonged recovery times after administration of BRIDION® are possible. Patients should be monitored for adequate recovery. Conditions associated with prolonged circulation time such as cardiovascular disease, old age, or edematous state (e.g., severe hepatic impairment) may be associated with longer recovery times.

Respiratory Function Monitoring 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 medicinal products used in the peri- and postoperative period could depress respiratory function and therefore ventilatory support might still be required.

Risk of Prolonged Neuromuscular Blockade
In clinical trials, a small number of patients experienced a delayed or minimal response to the administration of BRIDION®. Adequate anesthetic management, including ventilation support is mandatory until the patient has adequately emerged from anesthesia.

Risk of Recurrence of Neuromuscular Blockade
Patients should be monitored for recurrence of neuromuscular blockade after reversal. Should neuromuscular blockade reoccur following extubation, adequate ventilation should be provided. 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 ADVERSE REACTIONS).

Hematologic

Effect on Hemostasis

Sugammadex doses up to 16 mg/kg were associated with limited (≤25%) and transient (≤1 hour) increases in the coagulation parameters activated partial thromboplastin time (aPTT) and prothrombin time international normalized ratio [PT(INR)] in healthy volunteers. In surgical patients 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 (see ACTION AND PHARMACOLOGY, **Clinical Safety Pharmacology** – Effect on Hemostasis).

In *in vitro* experiments additional aPTT and PT (INR) prolongations were noted for sugammadex in combination with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran up to ~25% and ~50% at C_{max} levels of sugammadex corresponding to 4 mg/kg and 16 mg/kg doses, respectively.

Since bleeding risk has not been studied systematically at higher doses than sugammadex 4 mg/kg, coagulation parameters should be carefully monitored according to routine clinical practice in patients with known coagulopathies and in patients using anticoagulants who receive a dose of sugammadex higher than 4 mg/kg.

Neurologic

Effects on Ability to Drive and Use Machines

BRIDION® is not expected to have an effect on alertness and concentration, or on the recovery from anesthetics. The patient's ability to drive and use machines must be assessed based on adequate recovery of motor strength and coordination, as well as mental alertness and concentration.

Use in Intensive Care Unit (ICU)

BRIDION® has not been investigated in the ICU setting.

Special Populations

Pregnant Women

Surgery: No clinical data are available for the use of BRIDION® in pregnant women undergoing surgery.

Labour and Delivery: No clinical data are available for the use of BRIDION® in women during labour and delivery.

A series of repeat-dose reproductive safety studies were conducted in rats and rabbits. No teratogenicity was found at any doses studied during embryo-fetal development studies. In a prenatal and postnatal study, increased postnatal loss was found in drug treatment groups. No

drug-related effects on parturition were observed. (See TOXICOLOGY, Reproductive Toxicology).

Nursing Women
Excretion of BRIDION™ in human milk has not been studied. BRIDION® is excreted into milk in rats with a maximum level of 0.22% of the dose per gram milk, which decreases when plasma levels decrease. Oral exposure via milk does not induce any effects on survival, body weight and physical or behavioral developmental parameters monitored in newborn rats in peri- and postnatal development studies.

Pediatrics (<18 years of age):
The safety and efficacy of BRIDION® in pediatric patients have not been established.

Elderly patients
In a clinical study in the elderly, after administration of BRIDION® at reappearance of T_2 following a rocuronium induced blockade, the median time to recovery of the $T_4/_{T1}$ ratio to 0.9 in adults (18-64 years) was 2.2 minutes, 2.6 minutes in elderly adults (65-74 years), and 3.6 minutes in very elderly adults (75 years or more). Even though the recovery times in elderly tend to be slower, the same dose recommendation as for adults should be followed.

Renal Impairment
For mild and moderate renal impairment (creatinine clearance between ≥30 and <80 mL/min), the dose recommendations are the same as for adults without renal impairment. BRIDION® is not recommended for use in patients with severe (CrCl <30 mL/min) renal impairment including those requiring dialysis (see ACTION AND PHARMACOLOGY – **Special Populations and Conditions** – Renal Impairment).

Hepatic impairment
BRIDION® is not metabolized nor excreted by the liver; therefore dedicated studies in patients with hepatic impairment have not been conducted. The dose recommendations are the same as for adults, as BRIDION® is mainly excreted renally. Recovery times may be prolonged (see WARNINGS AND PRECAUTIONS). In patients with hepatic impairment accompanied by coagulopathy, hemostasis may be affected (see WARNINGS AND PRECAUTIONS – Effect on hemostasis).

Cardiac Patients
In patients with a history of cardiac disease (e.g., patients with ischemic heart disease, chronic heart failure, or arrhythmia) no dosage adjustment is necessary. General caution is advised as these patients are more vulnerable (see ACTION AND CLINICAL PHARMACOLOGY, **Cardiac Patients**).

Pulmonary Patients
In patients with a history of pulmonary complications, no dosage adjustment is necessary. General caution is advised as these patients are more vulnerable (see ACTION AND CLINICAL PHARMACOLOGY, **Pulmonary Patients**).

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

BRIDION® was studied in healthy volunteers and surgical patients undergoing general anesthesia to reverse the neuromuscular blockade induced with rocuronium or vecuronium, in comparison with placebo or other reversal agents. The causality of adverse events is sometimes difficult to assess in these patients. The identified Serious Adverse Drug Reactions caused by BRIDION® include anaphylaxis and hypersensitivity (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, **Serious Warnings and Precautions**, **Hypersensitivity Reactions**, and ACTION AND CLINICAL PHARMACOLOGY, **Clinical Safety Pharmacology**) and marked bradycardia (see WARNINGS AND PRECAUTIONS, **Cardiovascular**).

In the placebo-controlled dataset, the overall frequencies of all Adverse Events (AEs) were 70.7% on rocuronium plus BRIDION® vs. 82.5% on rocuronium plus placebo; 88.7% on vecuronium plus BRIDION® vs. 95.2% on vecuronium plus placebo. The individual AEs that occurred in at least 2.0% of BRIDION® subjects and at least twice as frequently as in placebo subjects included cough (4.7% BRIDION®, 2.0% placebo), airway complication of anesthesia (3.9% BRIDION®, 0% placebo), anesthetic complication (3.4% BRIDION®, 0.2% placebo), procedural hypotension (3.3% BRIDION®, 1.7% placebo) and procedural complication (2.0% BRIDION®, 0.6% placebo). In the active-controlled dataset, the overall AEs were 79.8% on rocuronium plus BRIDION® vs. 84.2% on rocuronium plus neostigmine; 93.8% on vecuronium plus BRIDION® vs. 94.0% on vecuronium plus neostigmine. The one AEs that occurred in at least 2.0% of BRIDION® patients and at least twice as frequently as in neostigmine patients was hypertension (3.8% BRIDION®, 1.5% neostigmine).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below reflect 1078 subjects exposed to BRIDION® and 544 to placebo in placebo-controlled trials, where subjects received anesthesia and/or neuromuscular blocking agent. The population was 18 to 91 years old, approximately equally divided between males and

females, mostly ASA (American Society of Anesthesiologists) Class 1-3, and predominantly Caucasian. Most subjects on BRIDION® received a single dose of 2 or 4 mg/kg.

The incidence of treatment-emergent adverse events was 74% with sugammadex and 82% for placebo. Treatment-emergent adverse events occurring in ≥2% of subjects treated with BRIDION® and at least twice as often compared to placebo for adult subjects who received anesthesia and/or neuromuscular blocking agent in pooled Phase I-III studies are presented in Table 1.

Table 1: Treatment-Emergent Adverse Events Occurring in at Least 2% of Bridion patients in Pooled Phase I-III Studies and Twice as Often in Comparison with Placebo

System Organ class	Treatment-Emergent Adverse Events (Preferred Term)	**BRIDION®** **(N=1078)** **n (%)**	**Placebo** **(N=544)** **n (%)**
Injury, poisoning and procedural complications	Airway complication of anesthesia	42 (4)	0 (0)
	Anesthetic complication	37 (3)	1 (<1)
	Procedural hypotension	36 (3)	9 (2)
	Procedural complication	22 (2)	3 (1)
Respiratory, thoracic and mediastinal disorders	Cough	51 (5)	11 (2)

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

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

Anesthetic complication:
Anesthetic complications, indicative of the restoration of neuromuscular function, include movement of a limb or the body or coughing during the anesthetic procedure or during surgery, grimacing, or suckling on the endotracheal tube. (See WARNINGS AND PRECAUTIONS, **Perioperative Considerations**, **Anesthetic Complication**)

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

The data described below reflect 871 subjects exposed to BRIDION® and 881 to neostigmine in

active-controlled trials, where subjects received anesthesia and a neuromuscular blocking agent. The population was 18 to 93 years old, approximately equally divided between males and females, all ASA (American Society of Anesthesiologists) Class 1-3, and predominantly Caucasian. Most subjects on BRIDION® received a single dose of 2 or 4 mg/kg.

The overall incidence of treatment-emergent adverse events was 84% with sugammadex and 87% for neostigmine. The one adverse event that occurred in at least 2.0% of BRIDION® patients and at least twice as frequently as in neostigmine patients was hypertension (3.8% BRIDION®, 1.5% neostigmine).

Hypersensitivity Reactions:
Hypersensitivity reactions, including anaphylaxis, have occurred in clinical trials in patients and healthy volunteers (see ACTION AND CLINICAL PHARMACOLOGY, **Clinical Safety Pharmacology**). In clinical trials of surgical patients these reactions were reported as infrequent (at least 1/1000, but less than 1/100) and for post-marketing reports the frequency is unknown. Anaphylaxis and anaphylactoid reactions have been reported in the post-marketing setting, including at doses in the range of 2 – 4 mg/kg. 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 (see WARNINGS AND PRECAUTIONS, **Hypersensitivity**; ACTION AND CLINICAL PHARMACOLOGY, **Clinical Safety Pharmacology**).

Recurrence of Neuromuscular Blockade:
In clinical studies including subjects treated with rocuronium or vecuronium, in which sugammadex was administered as directed (N=2022), recurrence of neuromuscular blockade as measured by neuromuscular monitoring or clinical signs, was reported in 0.20% patients.

Bronchospasm
In one dedicated clinical trial and in post-marketing data, in patients with a history of pulmonary complications, bronchospasm was reported as a possibly related adverse event.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of BRIDION®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders: Cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex (see WARNINGS AND PRECAUTIONS). Other cardiac rhythm abnormalities have included atrial fibrillation, atrioventricular block, cardiac/cardiorespiratory arrest, ST segment changes, supraventricular

tachycardia/ extrasystoles, tachycardia, ventricular fibrillation, and ventricular tachycardia.

General Disorders and Administration Site Conditions: Cases of BRIDION® not having the intended effect.

Immune System Disorders: Hypersensitivity events including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, and Type 1 hypersensitivity have been reported.

Respiratory, Thoracic, and Mediastinal Disorders: Events of laryngospasm, dyspnea, wheezing, pulmonary edema, and respiratory arrest have been reported.

DRUG INTERACTIONS

Overview

The information reported is based on binding affinity between BRIDION® and other drugs, preclinical experiments, simulations of a Pharmacokinetic-Pharmacodynamic (PK-PD) model and clinical studies. Based on these data, no clinically significant pharmacodynamic interaction with other drugs are expected, with the exception of toremifene, fusidic acid and hormonal contraceptives. For these drugs, a clinical relevant interaction could not be excluded. Toremifene is not available in Canada.

No clinically relevant interactions were reported during clinical development including with anticholinesterases, such as neostigmine, pyridostigmine, and edrophonium, or muscarinic blockers, such as glycopyrrolate and atropine.

Drug-Drug Interactions

Potential Interactions that Potentiate the 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 neuromuscular blockade. Refer to the product monograph of rocuronium or vecuronium for a list of the specific drugs which potentiate neuromuscular blockade. In case recurrence of neuromuscular blockade is observed, the patient may require mechanical ventilation.

Interactions Potentially Affecting the Efficacy of BRIDION® (see ACTION AND CLINICAL PHARMACOLOGY)

- Displacement interactions
  Pharmacokinetic-pharmacodynamic modeling indicated that administration of certain drugs after BRIDION®, could displace rocuronium or vecuronium from BRIDION®. As a result, recurrence of neuromuscular blockade might be observed. In this situation, the patient may require mechanical ventilation. Administration of the drug which caused displacement should be stopped in case of an infusion. The risk of displacement reactions will be at its highest during the period representing 3 times the half-life of BRIDION®.

- For the following drugs, displacement interactions could not be excluded:

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

  Intravenous Administration of Fusidic Acid

  The use of fusidic acid in the pre-operative phase may give some delay in the recovery of the T_4/T_1 ratio to 0.9. However, no recurrence of neuromuscular blockade is expected in the post-operative phase, since the infusion rate of fusidic acid is over a period of several hours and the blood levels are cumulative over 2-3 days. Interactions with topical products containing fusidic acid are not expected.

Interactions Potentially Affecting the Efficacy of Other Drugs (see also ACTION AND CLINICAL PHARMACOLOGY)

- Capturing interactions
  Pharmacokinetic-pharmacodynamic modeling indicated that administration of BRIDION®-may result in binding (capturing) to certain drugs. As a result, these drugs could become less effective due to a lowering of the (free) plasma concentrations.

  In this situation, 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 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** contraceptives containing a progestogen. Capturing interactions with an estrogen, namely ethinyl estradiol, are not expected to be clinically relevant. 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 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.

Drug-Laboratory Interactions

Interference with Laboratory Tests

BRIDION® may interfere with the serum progesterone assay. Interference with the test was observed at sugammadex plasma concentrations of 100 µg/mL which is only observed up to a maximum of 30 minutes after a 16 mg/kg dose. BRIDION® is not expected to interfere with an ethinyl estradiol assay.

DOSAGE AND ADMINISTRATION

Dosing Considerations

1) BRIDION® should be administered by trained healthcare providers familiar with the use, actions, characteristics, and complications of neuromuscular blocking agents (NMBA) and neuromuscular block reversal agents.

2) Doses and timing of BRIDION administration should be based on monitoring for twitch responses and the extent of spontaneous recovery that has occurred.

3) The recommended dose of BRIDION® does not depend on the anesthetic regimen, but rather on the level of neuromuscular blockade to be reversed. The anesthetic regimen may affect the recovery of the respiratory function and the reversal of the neuromuscular blockade independent of the reversal with BRIDION®.

4) BRIDION® should be used only for reversal of neuromuscular blockade induced with rocuronium or vecuronium. Its use to reverse neuromuscular blockade induced by other steroidal neuromuscular blockers is not recommended. It does not reverse the blockade induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds (e.g. atracurium and cisatracurium).

Recommended Dose and Dosage Adjustment

Adults

BRIDION® can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade to recovery defined as a train-of-four (TOF) (T_4/T_1) ratio of 0.9. The dose calculation is based on actual body weight. (see CLINICAL TRIALS and ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics).

A dose of 2.0 mg/kg BRIDION® is recommended when spontaneous recovery has reached the reappearance of T_2 (moderate blockade) following rocuronium or vecuronium induced neuromuscular blockade.

A dose of 4.0 mg/kg BRIDION® is recommended when spontaneous recovery has reached 1-2 post-tetanic counts (PTC), and there is no twitch response to train-of-four (TOF) stimulation (deep blockade) following administration of rocuronium or vecuronium induced neuromuscular blockade.

A dose higher than 4 mg/kg BRIDION® is not recommended for routine reversal of neuromuscular blockade induced by rocuronium or vecuronium, as it has not been studied and is possibly associated with higher incidence of hypersensitivity reactions.

Table 2: BRIDION® Dosing Guide

BRIDION® Dosing Guide	
Moderate blockade (Reappearance of second twitch [T_2] on TOF)	**2 mg/kg**
Deep blockade (1-2 post-tetanic counts [PTCs]), TOF-count 0	**4 mg/kg**

Urgent reversal: A dose of 16 mg/kg BRIDION® is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of a single dose of 1.2 mg/kg rocuronium for intubation. The efficacy of 16 mg/kg BRIDION for such use was studied in surgical patients without airway emergency. The efficacy of the 16 mg/kg dose of BRIDION® following administration of vecuronium has not been studied (see ACTION AND CLINICAL PHARMACOLOGY, **Clinical Pharmacology**)

This dose is associated with a 1-2% risk of an anaphylaxis in addition to higher frequencies of other less serious hypersensitivity reactions in studies of healthy volunteers (see ACTION AND CLINICAL PHARMACOLOGY, **Clinical Safety Pharmacology**).

Waiting Times for Re-Administration of Neuromuscular Blocking Agents for Intubation Following Reversal with BRIDION®:

A minimum waiting time is necessary before administration of a steroidal neuromuscular blocking agent after administration of BRIDION®. Recommendations are based upon a clinical study in healthy volunteers and simulations from a PK-PD model; the actual clinical patient response may vary significantly (see ACTION AND CLINICAL PHARMACOLOGY, **Clinical Pharmacology**).
If neuromuscular blockade is required before the recommended waiting time has elapsed, use a nonsteroidal neuromuscular blocking agent. 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.

For re-administration of rocuronium and vecuronium, the suggested minimum waiting time is outlined in the table below.

Table 3. Re-administration of Rocuronium or Vecuronium after Reversal (up to 4 mg/kg BRIDION)

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

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

For re-administration of rocuronium or administration of vecuronium after reversal of rocuronium with 16 mg/kg BRIDION®, a waiting time of 24 hours is suggested.

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 reversal with up to 4 mg/kg BRIDION® 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.

Administration

BRIDION® should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds into an existing intravenous line. The infusion line should be adequately flushed (e.g. with 0.9 % sodium chloride) between administration of BRIDION® and other drugs. Examine the site of intravenous line for any signs of leakage.

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 and 0.9% sodium chloride

and isolyte P with 5% dextrose.

BRIDION® must not be mixed with other medicinal products except those listed above. Physical incompatibility was observed with verapamil, ondansetron and ranitidine.

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, BRIDION® was tolerated well in doses up to 96 mg/kg. BRIDION® can be removed using hemodialysis with a high flux filter, but not with a low flux filter. Based upon clinical studies, BRIDION® concentrations in plasma are reduced by about 70% after a 3 to 6-hour dialysis session.

For management of a suspected drug overdose, contact your regional Poison Control Centre for the latest information.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BRIDION® is a modified gamma cyclodextrin which is a Selective Relaxant Binding Agent. BRIDION® encapsulates the neuromuscular blocking agents (NMBA) rocuronium and vecuronium and forms a complex with these agents in plasma. Following administration of BRIDION®, a shift in the concentration gradient of the NMBA between the neuromuscular junction and plasma causes a redistribution of the NMBA away from the nicotinic receptor. It thereby reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium or vecuronium.

Pharmacodynamics

BRIDION® 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-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 anesthetised subjects

Distribution:
The observed steady-state volume of distribution of sugammadex is 11 to 14 liters 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.

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

Special Populations and Conditions

Renal impairment and Geriatrics:
In a pharmacokinetic study comparing patients with severe renal impairment to patients with normal renal function, sugammadex levels in plasma were similar during the first hour after dosing and thereafter the levels decreased faster in the control group. Total exposure to sugammadex was prolonged, leading to 17-fold higher exposure in patients with severe renal impairment. Low concentrations of sugammadex are detectable for at least 48 hours post-dose in patients with severe renal insufficiency.

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

Population pharmacokinetic analysis indicated that, beyond the effects of a decreased creatinine clearance, increased age has limited impact on sugammadex PK parameters (see WARNINGS AND PRECAUTIONS).

Predicted pharmacokinetic parameters of sugammadex by age group and renal function based on compartmental modeling are presented in Table 4 .

Table 4: Summary of Sugammadex Pharmacokinetic Parameters Stratified by Age and Renal Function

Selected patient characteristics				**Mean Predicted PK parameters (CV*%)**		
Demographics	Renal function Creatinine clearance (mL/min)			Clearance (mL/min)	Volume of distribution at steady state (L)	Elimination half-life (hr)
Adult	Normal		100	88 (22)	12	2 (21)
40 yrs	Impaired	Mild	50	51 (22)	13	4 (22)
75 kg		Moderate	30	31 (23)	14	6 (23)
		Severe	10	9 (22)	14	19 (24)
Elderly	Normal		80	75 (23)	12	2 (21)
75 yrs	Impaired	Mild	50	51 (24)	13	3 (22)
75 kg		Moderate	30	31 (23)	14	6 (23)
		Severe	10	9 (22)	14	19 (23)

*CV = coefficient of variation

Cardiac Patients

One trial of 76 patients who were diagnosed with or have a history of cardiac disease (e.g., patients with ischemic heart disease, chronic heart failure, or arrhythmia) of primarily NYHA (New York Heart Association) Class II investigated time to recovery from neuromuscular blockade induced by rocuronium 0.6 mg/kg following administration of 2 mg/kg or 4 mg/kg BRIDION given at the reappearance of T_2. The trial showed that the median time to recovery of the T4/T1 ratio to 0.9 was 1.7 minutes and 1.3 minutes, respectively, in the 2 mg/kg and 4 mg/kg BRIDION dose groups. This is similar to the median values observed in the other trials; therefore, no dosage adjustment is necessary.

Pulmonary Patients

One trial of 77 patients who were diagnosed with or have a history of pulmonary complications investigated the time to recovery from neuromuscular blockade induced by rocuronium (0.6 mg/kg) following administration of 2 mg/kg or 4 mg/kg BRIDION given at the first signs of recovery (reappearance of T_2). The trial showed that for these patients the median time to recovery of the T4/T1 ratio to 0.9 was 2.1 minutes after a dose of 2 mg/kg BRIDION and 1.9

minutes after a dose of 4 mg/kg BRIDION. This is similar to the median values observed in the other trials; therefore, no dosage adjustment is necessary.

Gender:
No gender differences were observed.

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

Demographics:
The analysis of the available clinical trial data found no significant differences in the BRIDION® pharmacokinetics or pharmacodynamics with respect to gender or ethnic origin.

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

Clinical Safety Pharmacology

Hypersensitivity Reactions:
A randomized, double-blind study examined the incidence of drug hypersensitivity reactions in healthy volunteers given up to 3 repeat doses of placebo (N=76), sugammadex 4 mg/kg (N=151) or sugammadex 16 mg/kg (N=148). Reports of suspected hypersensitivity were adjudicated by a blinded committee. The incidence of adjudicated hypersensitivity was 1.3%, 6.6% and 9.5% in the placebo, sugammadex 4 mg/kg and sugammadex 16 mg/kg groups, respectively. There were no reports of anaphylaxis after placebo or sugammadex 4 mg/kg. There was a single case of adjudicated anaphylaxis after the first dose of sugammadex 16 mg/kg (incidence 0.7%).There was no evidence of increased frequency or severity of hypersensitivity with repeat dosing. 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%).

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

Cardiac Electrophysiology
A randomized, double-blind, placebo- and positive-controlled five-period crossover study was

performed to investigate the effect of BRIDION® on ECG intervals in healthy subjects (N=61). BRIDION® administered at single intravenous doses of 4 mg/kg and 32 mg/kg did not have clinically relevant effects on the QTc interval, the QRS duration, the PR interval, or ventricular heart rate.

Effect on Hemostasis
In a randomized, controlled clinical trial in surgical patients undergoing major orthopedic surgery while being treated with an anticoagulant (N=1184), treatment with 4 mg/kg sugammadex was not associated with an increased bleeding risk or blood loss as compared with usual treatment. The rate of adjudicated bleeding events within 24 hours was 2.9% for sugammadex and 4.1% for usual care.

For aPTT and PT(INR), a small (5.5% and 3.0%, respectively) and transient increase (within 1 hour after administration) was associated with sugammadex treatment, which, however, did not translate into an increase in the clinical risk for bleeding or blood loss. The rate of post-operative anemia was 21% for sugammadex and 22% for usual care; the mean post-operative changes in hemoglobin concentrations using the bleeding index were −16 g/L for sugammadex and −17 g/L for usual care; the mean 24-hour drainage volume was 0.46 L for sugammadex and 0.48 L for usual care, and the need for any post-operative transfusion was 37% for sugammadex and 39% for usual care.

Clinical Pharmacology

Urgent Reversal of Neuromuscular Blockade after Rocuronium
In order to simulate a clinical scenario requiring urgent reversal of neuromuscular blockade 3 minutes after rocuronium, a multicenter randomized, parallel-group, comparative, active-controlled, safety-assessor blinded study was conducted in 110 patients (64 women and 46 men, the majority were Caucasian and ASA class 1 and 2, median weight was 70 kg, and the median age was 43 years). Time to recovery from neuromuscular blockade induced by succinylcholine compared with recovery from neuromuscular blockade induced by rocuronium followed 3 minutes later with BRIDION® was assessed. Patients underwent surgical procedures under general anesthesia requiring a short duration of neuromuscular relaxation with the use of rocuronium or succinylcholine and requiring endotracheal intubation. The laparoscopic or open surgical procedures were mainly gynecological, orthopedic, or reconstructive in nature. Recovery to T_1 of 10% after neuromuscular blockade induced by 1.2 mg/kg rocuronium reversed at 3 minutes by 16 mg/kg BRIDION® was compared to spontaneous recovery after a neuromuscular blockade induced by 1 mg/kg succinylcholine.

Recovery to T_1 of 10% (relative to the time of administration of rocuronium or succinylcholine) was faster in the rocuronium/BRIDION® group compared with succinylcholine alone (Table 5).

Table 5: Time (minutes) from Start of Administration of Rocuronium or Succinylcholine to Recovery of T_1 to 10%

	Treatment Regimen	
	Rocuronium (1.2 mg/kg) and BRIDION® (16 mg/kg)	**Succinylcholine (1 mg/kg)**
N	55	55
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median (Range)	4.2 (3.5 – 7.7)	7.1 (3.8 – 10.5)

The mean time to recovery of T_1 to 90% was also assessed from the start of rocuronium or succinylcholine. This trial showed that the mean time was 6.2 minutes in the rocuronium/BRIDION® group and 10.9 minutes in the succinylcholine group. The data did not fit the normal distribution and recovery in some cases was prolonged.

Residual Neuromuscular Blockade

A multicenter, randomized, parallel-group, comparative, active-controlled, safety-assessor blinded, anesthesiologist-TOF-Watch® SX blinded study comparing the T_4/T_1 ratio at time of tracheal extubation enrolled 100 patients (60 women and 40 men, the majority were Caucasian and ASA class 2, median weight was 78 kg, and the median ages in the BRIDION® and neostigmine groups were 51 and 54 years, respectively). Patients underwent elective open abdominal surgical procedures that required general anesthesia. The surgical procedures were mainly gastrointestinal, gynecological, hernia repairs, or urological in nature. Patients were randomly assigned to the BRIDION® or neostigmine group. Patients received a single intubating bolus dose of 0.6 mg/kg rocuronium and maintenance dose(s) of 0.15 mg/kg rocuronium as necessary. At the end of the surgical procedure, the neuromuscular blockade was reversed with a single bolus dose of 4 mg/kg BRIDION® at 1-2 PTCs or with a single bolus dose of 50 mcg/kg neostigmine administered as per standard of care after the last dose of rocuronium.

The frequency of T_4/T_1 ratio at tracheal extubation by treatment group is shown in Table 6.

Table 6: Frequency (%) of T_4/T_1 Ratio at Tracheal Extubation by Treatment Group

T_4/T_1 Ratio at Tracheal Extubation*	Treatment Group	
	BRIDION® (4 mg/kg) N=43	Neostigmine (50 mcg/kg) N=38
T_4/T_1 Ratio $\leq$ 0.6	1 (2.3)	10 (26.3)
0.6 < T_4/T_1 Ratio $\leq$ 0.7	0 (0.0)	5 (13.2)
0.7 < T_4/T_1 Ratio $\leq$ 0.8	0 (0.0)	5 (13.2)
0.8 < T_4/T_1 Ratio < 0.9	1 (2.3)	6 (15.8)
0.9 $\geq$ T_4/T_1 Ratio	41 (95.4)	12 (31.6)

*Includes results from subjects with available T_4/T_1 ratio data at the time of extubation.

Waiting Times for Re-administration with Neuromuscular Blocking Agents (NMBA) after Reversal with BRIDION™

If re-administration of a neuromuscular blocking agent is required after reversal with BRIDION®, waiting times should be based on the dose of BRIDION®, and the renal function of the patient. A clinical study supporting re-administration of rocuronium (1.2 mg/kg) and vecuronium (0.1 mg/kg) following administration of 4 mg/kg BRIDION® was conducted in healthy subjects, where the time at which re-administration of rocuronium and vecuronium was varied. After re-use of rocuronium (1.2 mg/kg), subjects showed fast onset times of neuromuscular block already after the shortest reuse time at 5 minutes following sugammadex reversal. After re-use of vecuronium (0.1 mg/kg), subjects showed fast onset times of neuromuscular block already after a reuse time of approximately 4 hours following sugammadex reversal. Simulations (PK-PD) for re-administration scenarios in which a second dose of neuromuscular blocking agent was administered following BRIDION® were performed for adults with normal renal function and patients with mild to moderate renal impairment. Based on these simulations, it was recommended that in patients with mild to moderate renal impairment the waiting time for re-use of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after routine reversal with sugammadex should be 24 hours, compared to 4 hours for those with normal renal function.

STORAGE AND STABILITY

Store between 15˚C to 30˚C. Protect from light. When not protected from light, the vial should be used within 5 days.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

BRIDION® is supplied as a solution for injection containing 100 mg/mL of sugammadex as sugammadex sodium (108.8 mg/mL). Vials contain a clear and colorless to slightly yellow-brown solution. The pH is between 7 and 8 and osmolality is between 300 and 500 mOsm/kg.

100 mg/mL sugammadex is equivalent to 108.8 mg/mL of sugammadex sodium with up to 7 mg/mL mono-OH derivative.

Each vial of BRIDION® contains the following inactive ingredients: hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection

Single use injection vials of hydrolytic resistant glass, type I JP/USP/Ph. Eur. closed with grey chlorobutyl rubber closures. The rubber closures are held in position on the glass vials by roll-on aluminium crimp-caps with a “flip-off” seal. The rubber stopper of the vial does not contain latex. Pack sizes contain presentations of 2 mL (10 vials) or 5 mL (10 vials).

PART II: SCIENTIFIC INFORMATION

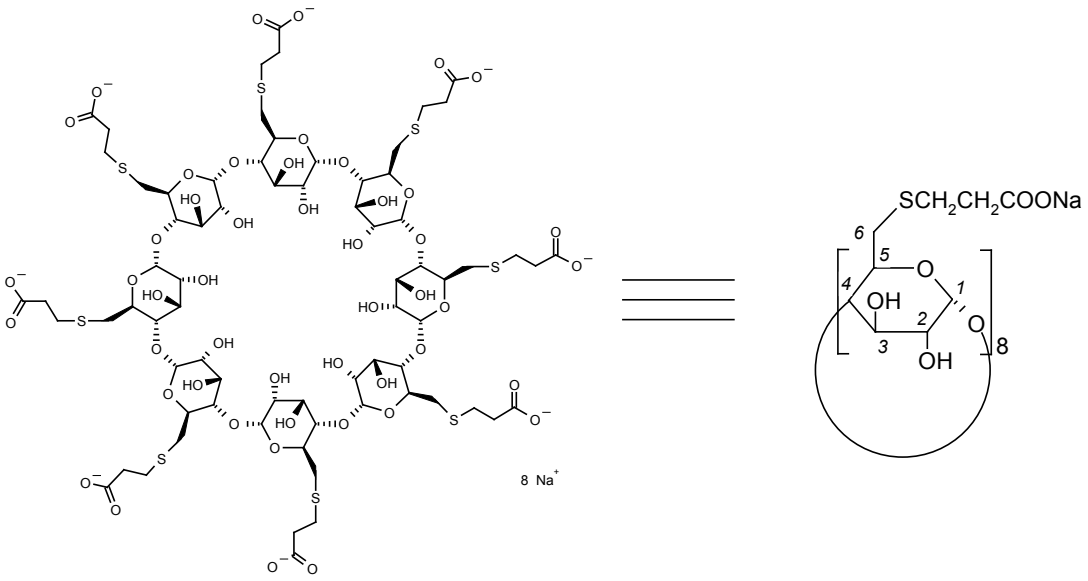
PHARMACEUTICAL INFORMATION

Common name: sugammadex sodium

Chemical name: $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octakis-S-(2-carboxyethyl)-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octathio-γ-cyclodextrin octasodium salt.

Molecular formula and molecular mass: $C_{72}H_{104}O_{48}S_8Na_8$, 2178.01

Structural formula:



BRIDION may contain up to 7 mg/mL of the mono OH-derivative of sugammadex. This derivative is chemically designated as *$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Heptakis-S-(2-carboxyethyl)-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptathio-γ-cyclodextrin sodium* salt (1:7) with a molecular weight of 2067.90.

Physicochemical properties:

Appearance: Sugammadex sodium is a white to off-white powder to grainy powder.
Melting point: Sugammadex sodium is a compound without a melting point or melting range. It decomposes at approximately 220°C.
Solubility: Sugammadex sodium is highly soluble in water
pH: Approximately 7.5

CLINICAL TRIALS

Study demographics and trial design

Table 7: Overview of Clinical Efficacy Trials

Protocol no. No. of centers (country) Trial status (start-end dates)	Trial objectives	Trial design	Dosage form , Dose, route, regimen, & duration	Diagnosis (inclusion criteria)	Enrolled/ treated/ completed, by trial arm	Gender[a] M/F	Age (yr) [a] Mean/median/range	Primary endpoint
19.4.301 13 centers (AT, BE, DE, ES, GB, IT, SE) Complete (November 2005 - March 2006)	To demonstrate faster recovery from rocuronium or vecuronium after reversal at reappearance of T_2 by 2.0 mg/kg sugammadex compared to 50 µg/kg neostigmine, and to evaluate the safety of 2.0 mg/kg sugammadex and 50 µg/kg neostigmine	Multi-center, randomized, parallel group, comparative, active controlled safety-assessor blinded, pivotal trial	Sugammadex: 100 mg/mL Dose: 2.0 mg/kg iv, single dose Rocuronium bromide: 10 mg/mL Dose: 0.6 mg/kg + maintenance doses, iv Vecuronium bromide: 2 mg/mL Dose: 0.1 mg/kg + maintenance doses, iv Water for Injection: 10 mL ampoules Neostigmine/ glycopyrrolate (premix): 2.5 mg/mL neostigmine and 0.5 mg/mL glycopyrrolate Dose: 50 µg/kg iv, single dose	ASA class 1 to 4, aged ≥18, scheduled for surgical procedure in supine position with a general anesthesia with the use of rocuronium or vecuronium	Rocuronium+ sugammadex: 49/48/47 Rocuronium+ neostigmine: 49/48/47 Vecuronium + sugammadex: 51/48/47 Vecuronium + neostigmine 49/45/44	Rocuronium + sugammadex : 31/17 Rocuronium + neostigmine: 24/24 Vecuronium + sugammadex : 26/22 Vecuronium + neostigmine 21/24	Rocuronium + sugammadex: 51/50/20-83 Rocuronium + neostigmine: 48/51/18-73 Vecuronium + sugammadex: 49/47/20-81 Vecuronium + neostigmine 50/51/21-81	Time from start administration of IP to recovery of the T_4/T_1 ratio to 0.9
19.4.302 8 centers (USA) Complete (November 2005 - November 2006)	To demonstrate faster recovery from rocuronium or vecuronium after reversal at a block of 1-2 PTCs by 4.0 mg/kg sugammadex compared with 70 µg/kg neostigmine and to evaluate the safety of a single dose of	Multicenter, randomized, parallel group, comparative, active controlled, safety-assessor blinded trial	sugammadex: 100 mg/mL Dose: 4.0 mg/kg iv, single dose Rocuronium bromide: 10 mg/mL Dose: 0.6 mg/kg + maintenance doses, iv Vecuronium bromide: 1 mg/mL Dose: 0.1 mg/kg + maintenance doses, iv	Aged 18 years old or older, ASA Class 1 to 4, scheduled to undergo an elective surgical procedure under general anesthesia in the supine position requiring the use of rocuronium or vecuronium for endotracheal	Rocuronium + sugammadex: 48/37/37 Rocuronium + neostigmine: 40/38/37 Vecuronium + sugammadex: 52/46/46 Vecuronium + neostigmine 42/36/35	Rocuronium + sugammadex : 16/21 Rocuronium + neostigmine: 17/21 Vecuronium + sugammadex : 17/29 Vecuronium + neostigmine 21/15	Rocuronium + sugammadex: 52/51/19-85 Rocuronium + neostigmine: 54/54/30-73 Vecuronium + sugammadex: 50/51/25-78 Vecuronium + neostigmine 57/60/29-77	Time from start administration of IP to recovery of the T_4/T_1 ratio to 0.9

Protocol no. No. of centers (country) Trial status (start-end dates)	Trial objectives	Trial design	Dosage form , Dose, route, regimen, & duration	Diagnosis (inclusion criteria)	Enrolled/ treated/ completed, by trial arm	Gender[a] M/F	Age (yr) [a] Mean/median/range	Primary endpoint
	4.0 mg/kg sugammadex and 70 µg/kg neostigmine		Sterile Water for Injection: 20 mL vials Neostigmine: 1 mg/mL Dose: 70 µg/kg iv, single dose Glycopyrrolate: 0.2 mg/mL Dose: 14 µg/kg iv, single dose	intubation and maintenance of neuromuscular blockade				
19.4.310 8 centers (ES, FR, GB, IT) Complete (Nov 2005-May 2006)	To show a faster recovery with sugammadex after rocuronium as compared to neostigmine after cisatracurium when administered at reappearance of T_2, to evaluate the safety of a single dose of 2.0 mg/kg sugammadex and 50 µg /kg neostigmine administered in adult subjects and to show a faster onset of neuromuscular blockade after 0.6 mg/kg rocuronium as compared to 0.15mg/kg cisatracurium.	Multi-center, randomized, safety-assessor blinded, parallel group, active controlled comparative trial.	Sugammadex: 100 mg/mL. Dose 2.0 mg/kg iv single dose Rocuronium bromide: 10 mg/mL. Dose 0.6 mg/kg + maintenance doses, iv Cisatracurium besilate: 2 mg/mL Dose 0.15 mg/kg + maintenance doses, iv Neostigmine/glycopyrrolate (premix): 2.5 mg/mL neostigmine and 0.5 mg/mL glycopyrrolate Dose 50 µg /kg, iv, single dose	Subjects of ASA class 1 to 4, above or equal to the age of 18 years; scheduled for surgical procedure under general anesthesia requiring neuromuscular relaxation with the use of rocuronium or cisatracurium; scheduled for surgical procedures in supine position	Rocuronium + sugammadex: 40/34/33 Cisatracurium + neostigmine: 44/39/39	Rocuronium + sugammadex : 14/20 Cisatracurium + neostigmine: 23/16	Rocuronium + sugammadex: 49/48/23-76 Cisatracurium + neostigmine: 42/40/22-69	Time from start administration of IP to recovery of the T_4/T_1 ratio to 0.9

[a] Treated

Study results

BRIDION® can be administered to reverse moderate to deep neuromuscular blockade induced with rocuronium or vecuronium bromide:

Reversal of Moderate Neuromuscular Blockade (Reappearance of T_2)

Study 19.4.301 was conducted in patients that underwent elective laparoscopic or open surgical procedures that required general anesthesia. The surgical procedures were mainly endocrine, ocular, ENT, abdominal (gynecological, colorectal, urological) orthopedic, vascular, or dermatological in nature. Patients were randomly assigned to the rocuronium or vecuronium group. After the last dose of rocuronium or vecuronium, at the reappearance of T_2, 2.0 mg/kg BRIDION® or 50 mcg/kg neostigmine was administered randomly as a single bolus injection. The time from start of administration of BRIDION® or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was assessed (Table 8).

Table 8: Time (minutes) from Administration of BRIDION® 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		p-value*
	BRIDION® (2.0 mg/kg)	Neostigmine (50 mcg/kg)	
Rocuronium			
N	48	48	
Geometric mean (95% CI)	1.5 (1.3 – 1.7)	18.5 (14.3 – 23.9)	<0.0001
Median (range)	1.4 (0.9-5.4)	17.6 (3.7-106.9)	
Vecuronium			
N	48	45	
Geometric mean (95% CI)	2.8 (2.3 – 3.4)	16.8 (12.9 – 21.9)	<0.0001
Median (range)	2.1 (1.2-64.2)	18.96 (2.9-76.2)	

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

Return of the T_4/T_1 ratio to 0.9 after the reappearance of T_2 was overall faster with BRIDION® 2 mg/kg as compared to neostigmine 50 mcg/kg in the setting of rocuronium or vecuronium-induced neuromuscular blockade (Figures 1 and 2). The data were out of normal distribution. They were log transformed for ANOVA analysis. Correlation between T_4/T_1 ratio $\geq$ 0.9 with clinically sufficient recovery from neuromuscular blockade endpoints is uncertain.

Figure 1: Time (Minutes) from Administration of BRIDION® or Neostigmine at the Reappearance of T_2 after Rocuronium to Recovery of the T_4/T_1 Ratio to 0.9

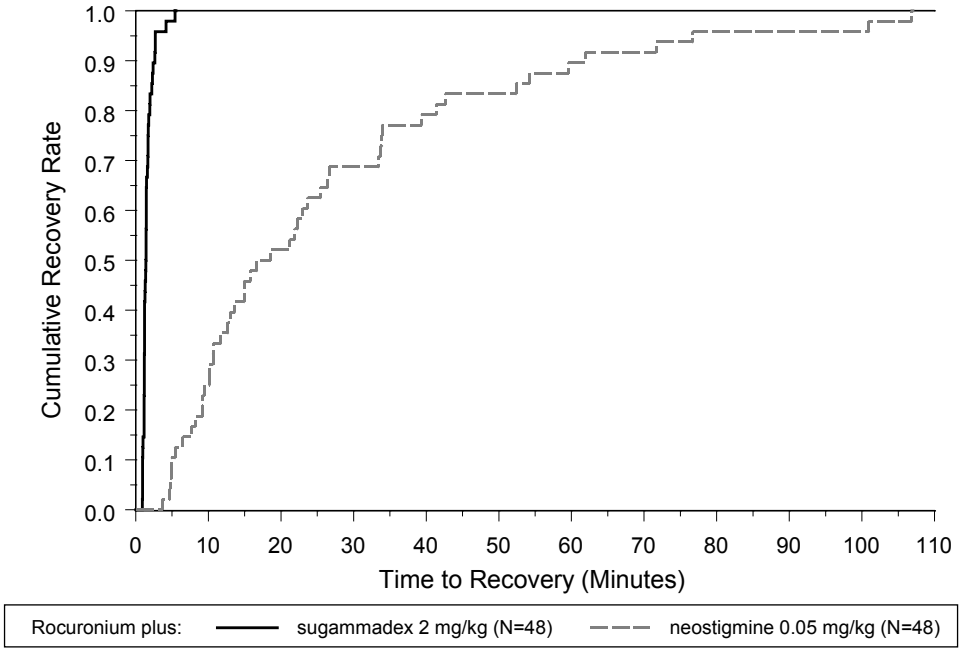
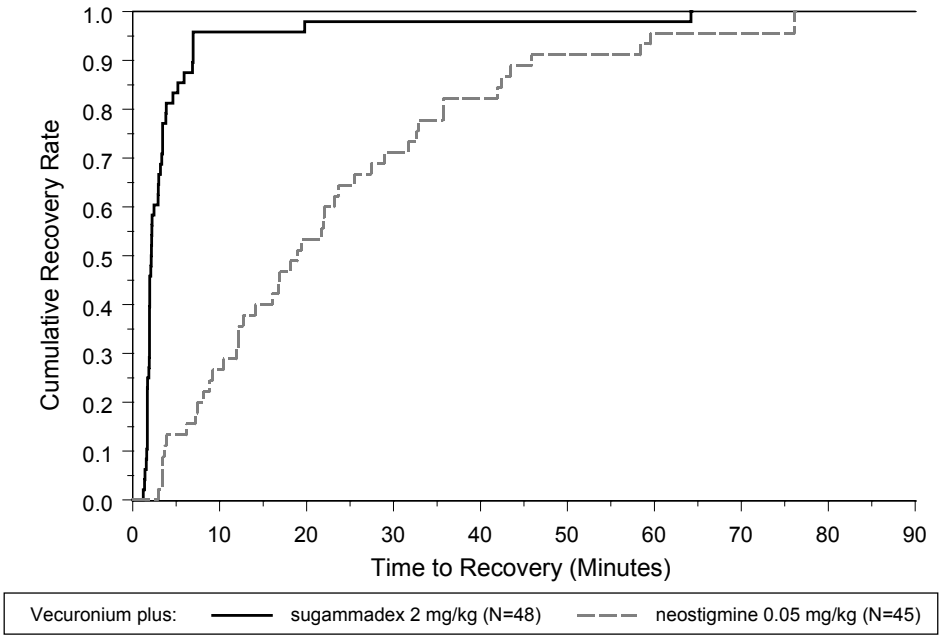


Figure 2: Time (Minutes) from Administration of BRIDION® or Neostigmine at the Reappearance of T_2 after Vecuronium to Recovery of the T_4/T_1 Ratio to 0.9



In study 19.4.310, reversal by BRIDION® of the neuromuscular blockade induced by rocuronium was compared to the reversal by neostigmine of the neuromuscular blockade induced by cis-atracurium. Patients underwent elective laparoscopic or open surgical procedures that required general anesthesia. The surgical procedures were mainly abdominal, ENT, orthopedic, or reconstructive in nature. At the reappearance of T_2 a dose of 2.0 mg/kg BRIDION® or 50 mcg/kg neostigmine was administered as a single bolus injection. The time from start of administration of BRIDION® or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was assessed (Table 9). Correlation between T_4/T_1 ratio ≥ 0.9 with clinically sufficient recovery from neuromuscular blockade endpoints is uncertain. Table 9 shows that BRIDION® provided faster reversal of neuromuscular blockade induced by rocuronium compared to neostigmine reversal of neuromuscular blockade induced by cis-atracurium.

Table 9: Time (minutes) from Administration of BRIDION® or Neostigmine at Reappearance of T_2 after Rocuronium or Cis-atracurium to Recovery of the T_4/T_1 Ratio to 0.9

Neuromuscular blocking agent	Treatment regimen		p-value*
	Rocuronium (0.6 mg/kg) and BRIDION® (2.0 mg/kg)	Cis-atracurium (0.15 mg/kg) and neostigmine (50 mcg/kg)	
N	34	39	
Geometric mean (95% CI)	2.0 (1.7-2.4)	8.8 (7.4-10.4)	<0.0001
Median (range)	1.9 (0.7-6.4)	7.2 (4.2-28.2)	

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

Reversal of Deep Neuromuscular Blockade

In study 19.4.302, patients underwent elective laparoscopic or open surgical procedures that required general anesthesia. The surgical procedures were mainly abdominal (gynecological, colorectal, urological), orthopedic, reconstructive, or neurological in nature. Patients were randomly assigned to the rocuronium or vecuronium group. After the last dose of rocuronium or vecuronium, at 1-2 PTCs, 4.0 mg/kg BRIDION® or 70 mcg/kg neostigmine was administered in a randomized order as a single bolus injection. The time from start of administration of BRIDION® or neostigmine to recovery of the TOF ($T_4/T_{1)}$ ratio to 0.9 was assessed (Table 10).

Table 10: Time (minutes) from Administration of BRIDION® or Neostigmine at Deep Neuromuscular Blockade (1-2 PTCs) after Rocuronium or Vecuronium to Recovery of the T_4/T_1 Ratio to 0.9

Neuromuscular blocking agent	Treatment regimen		p-value*
	BRIDION® (4.0 mg/kg)	Neostigmine (70 mcg/kg)	
Rocuronium			
N	37	37	
Geometric mean (95% CI)	2.9 (2.5-3.4)	50.4 (43.5-58.4)	<0.0001
Median (range)	2.7 (1.2-16.1)	49.0 (13.3-145.7)	
Vecuronium			
N	47	36	
Geometric mean (95% CI)	4.5 (3.3-6.0)	66.2 (55.6-78.9)	<0.0001
Median (range)	3.3 (1.4-68.4)	49.9 (46.0-312.7)	

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

BRIDION® 4 mg/kg provided faster reversal of deep neuromuscular blockade induced by rocuronium or vecuronium compared to neostigmine 70 mcg/kg (Figures 3 and 4). The data were out of normal distribution. They were log transformed for ANOVA analysis. Correlation between T_4/T_1 ratio ≥ 0.9 with clinically sufficient recovery from neuromuscular blockade endpoints is uncertain.

Figure 3: Time (Minutes) from Administration of BRIDION® or Neostigmine at 1 to 2 PTCs after Rocuronium to Recovery of the T_4/T_1 Ratio to 0.9

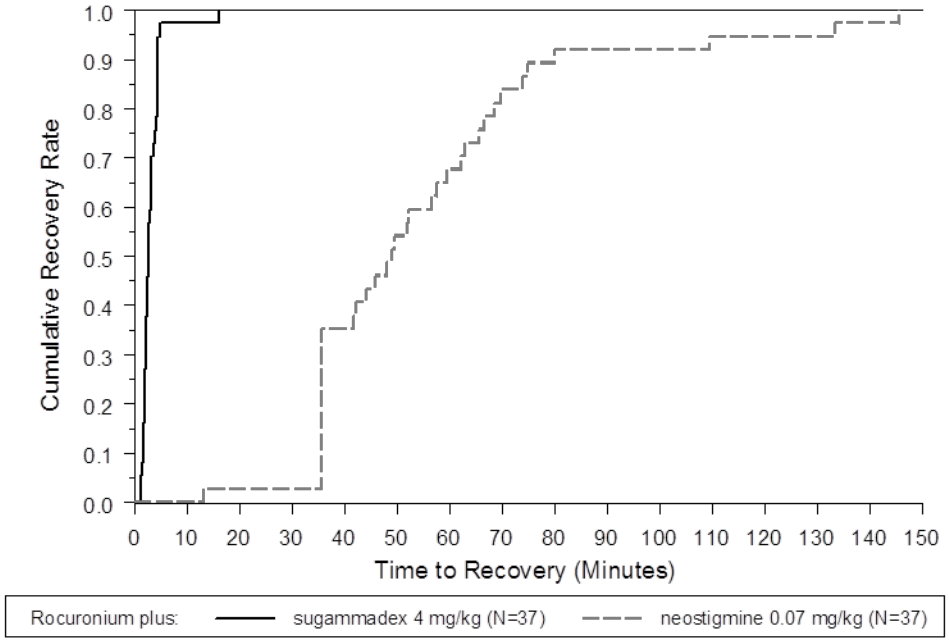
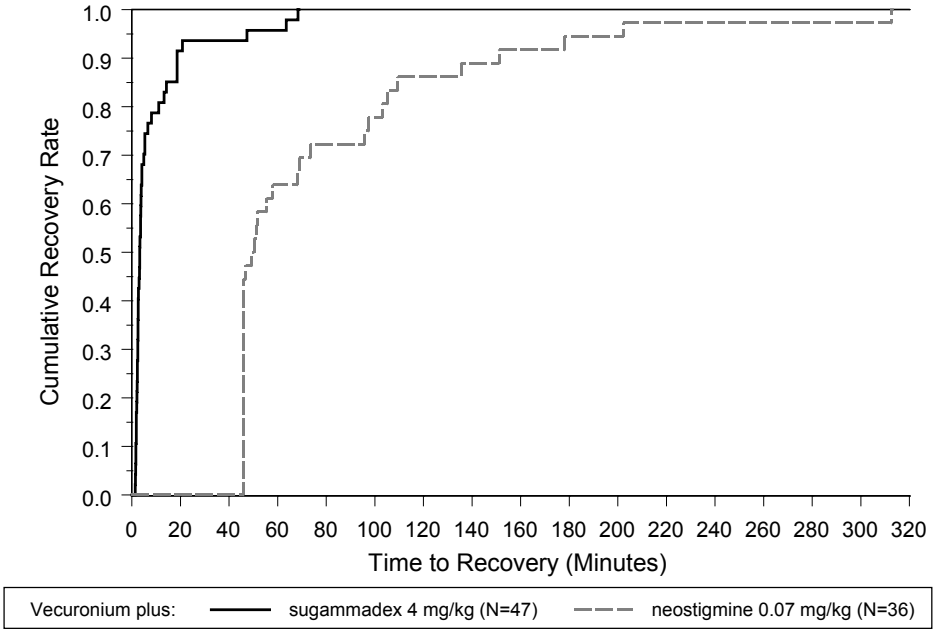


Figure 4: Time (Minutes) from Administration of BRIDION® or Neostigmine at 1 to 2 PTCs after Vecuronium to Recovery of the T_4/T_1 Ratio to 0.9



DETAILED PHARMACOLOGY

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not done given the intended use of sugammadex and absence of genotoxic potential. Sugammadex did not induce gene mutations or chromosome aberrations in vivo or in vitro. Sugammadex did not impair male or female fertility in rats at 500 mg/kg/day representing approximately 6- to 50-fold greater exposures as compared to human exposures at recommended dose levels. Further, no morphological alterations of male and female reproductive organs were noted in 4-week toxicity studies in rats and dogs. Sugammadex was not teratogenic in rat and rabbit.

Repeat Dose Toxicology

Sugammadex is rapidly cleared in preclinical species, although some sugammadex is observed in bone and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex has no adverse effect on tooth color or bone quality, bone structure or bone metabolism. Sugammadex has no effect on fracture repair and fracture remodeling in rats.

Sugammadex is well tolerated in repeat dose, intravenous toxicology studies of 4-weeks duration in rats at 500 mg/kg/day and in dogs at 250 mg/kg/day. Vacuolation of renal tubular epithelium and/or transitional epithelium of the urinary bladder is consistent with high-dose, parenteral administration of a cyclodextrin in nonclinical species. However, daily administration of sugammadex has no effect on renal function and does not alter tissue morphology.

Safety Pharmacology

Bone and teeth retention of sugammadex occurred in rats after intravenous injection, with mean half-lives of 172 and 8 days, respectively. Sugammadex bound to hydroxyapatite in an in vitro study and distributed in the bone formation area where hydroxyapatite is present for mineralization in vivo.

In adult rat bone toxicity studies, a single dose of sugammadex at 2000 mg/kg (approximately 24 times the maximum recommended human dose (MRHD) of 16 mg/kg by AUC comparison) administered to adult rats caused a slight increase in bone resorption, but had no effect on teeth color. No adverse bone effects were seen following a single dose of sugammadex at 500 mg/kg (4 times the MRHD dose of 16 mg/kg based on plasma AUC comparison).

In a bone repair study, adult rats were treated with intravenous sugammadex weekly for 6 weeks at 0, 30, 120, and 500 mg/kg (approximately 0.4, 1, and 6 times the MRHD, respectively, by AUC comparison). Based on histological data, high dose animals with post-fracture treatment, showed a statistically significant increase in callus formation and decrease in bone formation, suggesting a potential for a slight delay in the bone healing process. However there were no statistically significant effects on bone volume or bone mineral density.

Reproductive Toxicology

A fertility and early embryonic development study in Sprague-Dawley rats in which male rats were treated daily for 29 days prior to mating and through the mating period and female rats were treated daily for 14 days prior to mating to Day 5 post-coitum via intravenous administration of sugammadex at 20, 100, and 500 mg/kg (0.2, 1, and 6 times the MRHD of 16 mg/kg, respectively, based on AUC comparison) did not show adverse effects on fertility.

In an embryofetal development study in rats, pregnant animals received daily intravenous administration of sugammadex at 0, 20, 100, and 500 mg/kg (0.2, 1, and 6-times the MRHD of 16 mg/kg/day, respectively, based on AUC comparison) during organogenesis (Gestational Days 6 - 17). No treatmentrelated maternal and embryofetal changes were observed.

In another embryofetal development study, pregnant New Zealand white rabbits received daily - intravenous administration of sugammadex at 0, 20, 65, 200 mg/kg (0.6, 2, and 8 times the MRHD, respectively, based on AUC comparison) during organogenesis (Gestational Days 6-18). Fetal body weight decreases (10 and 14%, respectively) were observed in the offspring at maternal doses of 65 mg/kg and 200 mg/kg. In addition, incomplete ossification of sternebra, and unossified 1st metacarpal were noted at a maternal dose of 200 mg/kg/day. Maternal toxicity was also observed at 200 mg/kg. Considering the observed effects of sugammadex on bone, it is possible that these findings may be attributable to drug. There was no evidence of teratogenicity at any dose.

Studies in Juvenile Animals

In a bone deposition study, sugammadex concentrations were significantly higher in juvenile rats compared to adult rats (13% vs. 3% of the administered dose, respectively) following a single intravenous (IV) dose at 30 mg/kg (0.3 times the MRHD based on adult AUC comparison).

In a juvenile animal bone toxicity study, 7-day old rats were dosed intravenously once daily for 28 days with 0, 30, 120, and 500 mg/kg sugammadex (approximately 0.1, 0.6, and 3 times the MRHD, respectively, by adult AUC comparison). Sugammadex at 120 and 500 mg/kg decreased ulna and femur bone lengths by approximately 3%, which did not recover after an 8-week treatment-free period. Reversible whitish discoloration and disturbance of enamel formation were also observed in the incisors at these dose levels. In molars, this effect was only observed at 500 mg/kg. The no-observed-effect-level (NOEL) was 30 mg/kg.

In a second juvenile animal bone toxicity study, 7-day old rats were dosed once weekly for 8 weeks with 0, 7.5, 30, and 120 mg/kg (up to 1.2 times the MRHD of 16 mg/kg based on adult AUC comparison). No adverse effects on bone or teeth were noted.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

BRIDION®
solution for injection,
100 mg/mL sugammadex (as sugammadex sodium)

Read this carefully. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BRIDION®.

Serious Warnings and Precautions

- This drug should be administered only by trained healthcare providers familiar with the use, actions, characteristics, and complications of neuromuscular blocking agents (NMBA) and neuromuscular block reversal agents.
- This drug may cause allergic reactions. Severe allergic or allergic-like reactions can be life threatening.

What is BRIDION® used for?
BRIDION® is used to help speed up the recovery of your muscles after an operation in adults.

How does BRIDION® work?
When you have surgery you are given drugs that help your muscles relax completely. These types of drugs are known as muscle relaxants. Rocuronium and vecuronium are a type of muscle relaxant that the doctor may give to you before your surgery. When your muscles are relaxed it makes it easier for the doctor to do the surgery. At the end of your surgery, BRIDION™ is given to help get rid of the effects of these muscles relaxants.

What are the ingredients in BRIDION® ?
Medicinal ingredients: sugammadex.

Non-medicinal ingredients: hydrochloric acid, sodium hydroxide, water for injection

BRIDION® comes in the following dosage forms:
Solution for Injection: 100 mg/mL

Do not use BRIDION® if you:

- are allergic to sugammadex or to any of the other ingredients in BRIDION®. Tell your doctor who will be giving you the anesthesia if you have any allergies. This includes any allergies to food or other drugs.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BRIDION®. Talk about any health conditions or problems you may have, including if you:

- have heart problems
- have liver disease or have had it in the past
- have fluid retention (edema)
- have kidney disease or have had it in the past or are on dialysis. This is important as BRIDION® is removed from your body by the kidneys. Tell your doctor who will be giving you the anesthesia if this applies to you.
- are pregnant or might be pregnant
- are breastfeeding
- have diseases which are known to give an increased risk of bleeding (trouble with blood clotting)
- have a history of airway or lung problems

Other warnings you should know about:

Driving and using machines: Your doctor will tell you when it is safe to drive or use machines after you have been given BRIDION®. BRIDION® is not expected to have an effect on alertness or concentration.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BRIDION®:

- toremifene (used to treat breast cancer)
- fusidic acid (used to treat infections)

It is important that you tell your doctor who will be giving you the anesthesia if you have recently taken these medicines.

BRIDION® can affect hormonal contraceptives used for birth control:
BRIDION™ can make birth control methods less effective because it reduces how much you get of the hormone progestogen. Tell your doctor if you are currently using any of the following:

- the 'Pill'
- vaginal ring
- implants
- hormonal Intra Uterine Device (IUD)

If you are:

- taking the "Pill" on the same day as BRIDION™ is given to you, follow the instructions for a missed dose in the Pill's package insert.
- using other **non-oral** contraceptive methods (for example a vaginal ring, implant or IUD, you should use an additional non-hormonal contraceptive method (such as a condom) for the next 7 days.

Effects on blood tests:
In general, BRIDION® does not have an effect on laboratory tests. However, it may change the results of a blood test for progesterone (a hormone).

How to take BRIDION®:
BRIDION™ will be given to you by a doctor who is trained in giving drugs used when you are having surgery. It is given through your vein as a single injection.

Usual dose:
Your doctor will determine the dose of BRIDION™ you need. It is based on your weight and how much the muscle relaxant drugs are still affecting you.

Usual dose: 2mg - 4 mg per kg of body weight. The doctor will determine exactly how much you will be given.

Overdose:
Your doctor will be monitoring you carefully. BRIDION® is for hospital use only.

Missed Dose:
Not applicable.

What are possible side effects from using BRIDION® ?

These are not all the possible side effects you may feel after you have been given BRIDION®. After your operation, if you experience any side effects that are not listed here or you notice any of your side effects getting worse, tell the doctor or nurse right away.

- Allergic reaction such as:
  - a rash or red skin
  - swelling of your tongue and/ or throat
  - shortness of breath
  - changes in blood pressure or heart rate, sometimes resulting in a serious decrease of blood pressure.
  - severe allergic or allergic-like reactions (anaphylaxis) that can be life threatening.
- Slow heart rate that can be life threatening.
- Complications during your procedure such as:
  - airway difficulties
  - changes in heart rate
  - coughing or moving.
  - light anesthesia that needs the attention of your doctor.
- Decreased blood pressure during the surgical procedure
- Return of muscle relaxation after the operation
- Shortness of breath due to muscle spasm of the airways (bronchospasm or laryngospasm)

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
The hospital will store BRIDION® according to the correct storage conditions.

If you want more information about BRIDION®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594

To report an adverse event related to BRIDION®, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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