

## **Package leaflet: Information for the user**

### **Bridion® 100 mg/mL solution for injection** sugammadex

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your anaesthetist or doctor.
- If you get any side effects, talk to your anaesthetist or other doctor. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Bridion is and what it is used for
2. What you need to know before Bridion is given
3. How Bridion is given
4. Possible side effects
5. How to store Bridion
6. Contents of the pack and other information

#### **1. What Bridion is and what it is used for**

##### **What Bridion is**

Bridion contains the active substance sugammadex. Bridion is considered to be a *Selective Relaxant Binding Agent* since it only works with specific muscle relaxants, rocuronium bromide or vecuronium bromide.

##### **What Bridion is used for**

When you have some types of operations, your muscles must be completely relaxed. This makes it easier for the surgeon to do the operation. For this, the general anaesthetic you are given includes medicines to make your muscles relax. These are called *muscle relaxants*, and examples include rocuronium bromide and vecuronium bromide. Because these medicines also make your breathing muscles relax, you need help to breathe (artificial ventilation) during and after your operation until you can breathe on your own again.

Bridion is used to speed up the recovery of your muscles after an operation to allow you to breathe on your own again earlier. It does this by combining with the rocuronium bromide or vecuronium bromide in your body. It can be used in adults whenever rocuronium bromide or vecuronium bromide is used.

It can be used in newborn babies, infants, toddlers, children, and adolescents (birth to 17 years) when rocuronium bromide is used.

#### **2. What you need to know before Bridion is given**

##### **You should not be given Bridion**

- if you are allergic to sugammadex or any of the other ingredients of this medicine (listed in section 6).

→ Tell your anaesthetist if this applies to you.

##### **Warnings and precautions**

Talk to your anaesthetist before Bridion is given

- if you have kidney disease or had in the past. This is important as Bridion is removed from your body by the kidneys.
- if you have liver disease or have had it in the past.

- if you have fluid retention (oedema).
- if you have diseases which are known to give an increased risk of bleeding (disturbances of blood clotting) or anticoagulation medication.

### **Other medicines and Bridion**

→ Tell your anaesthetist if you are taking, have recently taken or might take any other medicines. Bridion may affect other medicines or be affected by them.

### **Some medicines reduce the effect of Bridion**

→ It is especially important that you tell your anaesthetist if you have recently taken:

- toremifene (used to treat breast cancer).
- fusidic acid (an antibiotic).

### **Bridion can affect hormonal contraceptives**

- Bridion can make hormonal contraceptives - including the 'Pill', vaginal ring, implants or a hormonal IntraUterine System (IUS) - less effective because it reduces how much you get of the progestogen hormone. The amount of progestogen lost by using Bridion is about the same as missing one oral contraceptive Pill.
  - 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 leaflet.
  - If you are using **other** hormonal contraceptives (for example a vaginal ring, implant or IUS) you should use an additional non-hormonal contraceptive method (such as a condom) for the next 7 days and follow the advice in the package leaflet.

### **Effects on blood tests**

In general, Bridion does not have an effect on laboratory tests. However, it may affect the results of a blood test for a hormone called progesterone. Talk to your doctor if your progesterone levels need to be tested on the same day you receive Bridion.

### **Pregnancy and breast-feeding**

→ Tell your anaesthetist if you are pregnant or might be pregnant or if you are breast-feeding.

You may still be given Bridion, but you need to discuss it first.

It is not known whether sugammadex can pass into breast milk. Your anaesthetist will help you decide whether to stop breast-feeding, or whether to abstain from sugammadex therapy, considering the benefit of breast-feeding to the baby and the benefit of Bridion to the mother.

### **Driving and using machines**

Bridion has no known influence on your ability to drive and use machines.

### **Bridion contains sodium**

This medicine contains up to 9.7 mg sodium (main component of cooking / table salt) in each mL. This is equivalent to 0.5% of the recommended maximum daily dietary intake of sodium for an adult.

## **3. How Bridion is given**

Bridion will be given to you by your anaesthetist, or under the care of your anaesthetist.

### **The dose**

Your anaesthetist will work out the dose of Bridion you need based on:

- your weight
- how much the muscle relaxant medicine is still affecting you.

The usual dose is 2-4 mg per kg body weight for patients of any age. A dose of 16 mg/kg can be used in adults if urgent recovery from muscle relaxation is needed.

**How Bridion is given**

Bridion will be given to you by your anaesthetist. It is given as a single injection through an intravenous line.

**If more Bridion is given to you than recommended**

As your anaesthetist will be monitoring your condition carefully, it is unlikely that you will be given too much Bridion. But even if this happens, it is unlikely to cause any problems.

If you have any further questions on the use of this medicine, ask your anaesthetist or other doctor.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. If these side effects occur while you are under anaesthesia, they will be seen and treated by your anaesthetist.

**Common side effects (may affect up to 1 in 10 people)**

- Cough
- Airway difficulties that may include coughing or moving as if you are waking or taking a breath
- Light anaesthesia - you may start to come out of deep sleep, so need more anaesthesia. This might cause you to move or cough at the end of the operation
- Complications during your procedure such as changes in heart rate, coughing or moving
- Decreased blood pressure due to the surgical procedure

**Uncommon side effects (may affect up to 1 in 100 people)**

- Shortness of breath due to muscle cramps of the airways (bronchospasm) occurred in patients with a history of lung problems
- Allergic (drug hypersensitivity) reactions - such as a rash, 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 can be life threatening.  
Allergic reactions were reported more commonly in healthy, conscious volunteers
- Return of muscle relaxation after the operation

**Frequency not known**

- Severe slowing of the heart and slowing of the heart up to cardiac arrest may occur when Bridion is administered

**Reporting of side effects**

If you get any side effects, talk to your anaesthetist or other doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Bridion**

Storage will be handled by healthcare professionals.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label after 'EXP'. The expiry date refers to the last day of that month.

Store below 30 °C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

After first opening and dilution, store at 2 to 8 °C and use within 24 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Bridion contains**

- The active substance is sugammadex.  
1 mL solution for injection contains sugammadex sodium equivalent to 100 mg sugammadex.  
Each vial of 2 mL contains sugammadex sodium equivalent to 200 mg sugammadex.  
Each vial of 5 mL contains sugammadex sodium equivalent to 500 mg sugammadex.
- The other ingredients are water for injections, hydrochloric acid 3.7% and/or sodium hydroxide.

### **What Bridion looks like and contents of the pack**

Bridion is a clear and colourless to slightly yellow solution for injection.

It comes in two different pack sizes, containing either 10 vials with 2 mL or 10 vials with 5 mL solution for injection.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder:** Merck Sharp & Dohme (UK) Limited, 120 Moorgate, London, EC2M 6UR, United Kingdom

**Manufacturer:** Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, The Netherlands.

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**This leaflet was last revised in January 2025.**

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### **The following information is intended for healthcare professionals only:**

For detailed information refer to the Summary of Product Characteristics (SmPC) of BRIDION.

### **Therapeutic indications and posology**

Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults.

For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in paediatric patients from birth to 17 years.

Sugammadex should only be administered by, or under the supervision of an anaesthetist.

The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of neuromuscular blockade (see SmPC, section 4.4).

#### *Adults*

#### Routine reversal:

A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the  $T_4/T_1$  ratio to 0.9 is around 3 minutes (see SmPC, section 5.1).

A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of  $T_2$  following rocuronium or vecuronium induced blockade. Median time to recovery of the  $T_4/T_1$  ratio to 0.9 is around 2 minutes (see SmPC, section 5.1).

Using the recommended doses for routine reversal will result in a slightly faster median time to recovery of the  $T_4/T_1$  ratio to 0.9 of rocuronium when compared to vecuronium induced neuromuscular blockade (see SmPC, section 5.1).

#### Immediate reversal of rocuronium-induced blockade:

If there is a clinical need for immediate reversal following administration of rocuronium a dose of 16 mg/kg sugammadex is recommended. When 16 mg/kg sugammadex is administered 3 minutes after a bolus dose of 1.2 mg/kg rocuronium bromide, a median time to recovery of the  $T_4/T_1$  ratio to 0.9 of approximately 1.5 minutes can be expected (see SmPC, section 5.1).

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

#### Re-administration of sugammadex:

In the exceptional situation of recurrence of neuromuscular blockade post-operatively (see SmPC, section 4.4) after an initial dose of 2 mg/kg or 4 mg/kg sugammadex, a repeat dose of 4 mg/kg sugammadex is recommended. Following a second dose of sugammadex, the patient should be closely monitored to ascertain sustained return of neuromuscular function.

#### Renal impairment:

The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis ( $\text{CrCl} < 30 \text{ mL/min}$ )) is not recommended (see SmPC, section 4.4).

#### Obese patients:

In obese patients, including morbidly obese patients (body mass index  $\geq 40 \text{ kg/m}^2$ ), the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed.

#### *Paediatric population (birth to 17 years of age)*

Bridion 100 mg/mL may be diluted to 10 mg/mL to increase the accuracy of dosing in the paediatric population (see SmPC, section 6.6).

#### Routine reversal:

A dose of 4 mg/kg sugammadex is recommended for reversal of rocuronium induced blockade if recovery has reached at least 1-2 PTC.

A dose of 2 mg/kg is recommended for reversal of rocuronium induced blockade at reappearance of  $T_2$  (see SmPC, section 5.1).

#### **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

#### **Special warnings and precautions for use**

As is normal post-anaesthetic practice following neuromuscular blockade, it is recommended to monitor the patient in the immediate post-operative period for untoward events including recurrence of neuromuscular blockade.

#### Monitoring respiratory function during recovery:

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

Should neuromuscular blockade reoccur following extubation, adequate ventilation should be provided.

#### Recurrence of neuromuscular blockade:

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade, an incidence of 0.20% was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence. The use of lower than recommended doses may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended (see SmPC, section 4.2 and section 4.8).

#### Effect on haemostasis:

In a study in volunteers doses of 4 mg/kg and 16 mg/kg of sugammadex resulted in maximum mean prolongations of the activated partial thromboplastin time (aPTT) by 17 and 22% respectively and prothrombin time international normalised ratio [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 data-base (N=3 519) and on a specific study in 1 184 patients undergoing hip fracture/major joint replacement surgery there was no clinically relevant effect of sugammadex 4 mg/kg alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications.

In *in vitro* experiments a pharmacodynamic interaction (aPTT and PT prolongation) was noted with vitamin K antagonists, unfractionated heparin, low molecular weight heparinoids, rivaroxaban and dabigatran. In patients receiving routine post-operative prophylactic anticoagulation this pharmacodynamic interaction is not clinically relevant. Caution should be exercised when considering the use of sugammadex in patients receiving therapeutic anticoagulation for a pre-existing or co-morbid condition.

An increased risk of bleeding cannot be excluded in patients:

- with hereditary vitamin K dependent clotting factor deficiencies;
- with pre-existing coagulopathies;
- on coumarin derivatives and at an INR above 3.5;
- using anticoagulants who receive a dose of 16 mg/kg sugammadex.

If there is a medical need to give sugammadex to these patients the anaesthesiologist needs to decide if the benefits outweigh the possible risk of bleeding complications taking into consideration the patients history of bleeding episodes and type of surgery scheduled. If sugammadex is administered to these patients monitoring of haemostasis and coagulation parameters is recommended.

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

**Table 1: Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg sugammadex):**

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

The onset of neuromuscular blockade may be prolonged up to approximately 4 minutes, and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes after re-administration of rocuronium 1.2 mg/kg within 30 minutes after sugammadex administration.

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

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

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

#### Renal impairment:

Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis (see SmPC, section 5.1).

#### 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 suckling of the tracheal tube).

If neuromuscular blockade is reversed, while anaesthesia is continued, additional doses of anaesthetic and/or opioid should be given as clinically indicated.

#### Marked bradycardia:

In rare instances, marked bradycardia has been observed within minutes after the administration of sugammadex for reversal of neuromuscular blockade. Bradycardia may occasionally lead to cardiac arrest. (see SmPC, section 4.8.) Patients should be closely monitored for haemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anti-cholinergic agents such as atropine should be administered if clinically significant bradycardia is observed.

#### Hepatic impairment:

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

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

Sugammadex has not been investigated in patients receiving rocuronium or vecuronium in the ICU setting.

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

Sugammadex should not be used to reverse block induced by **nonsteroidal** neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.

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

#### Delayed recovery:

Conditions associated with prolonged circulation time such as cardiovascular disease, old age (see SmPC, section 4.2 for the time to recovery in elderly), or oedematous state (e.g., severe hepatic impairment) may be associated with longer recovery times.

#### Drug hypersensitivity reactions:

Clinicians should be prepared for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions (see SmPC, section 4.8).

#### Sodium:

This medicinal product contains up to 9.7 mg sodium per mL, equivalent to 0.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

#### **Interaction with other medicinal products and other forms of interaction**

The information in this section is based on binding affinity between sugammadex and other medicinal products, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking agents and the pharmacokinetic interaction between neuromuscular blocking agents and sugammadex. Based on these data, no clinically significant pharmacodynamic interaction with other medicinal products is expected, with exception of the following:

For toremifene and fusidic acid displacement interactions could not be excluded (no clinically relevant capturing interactions are expected).

For hormonal contraceptives a clinically relevant capturing interaction could not be excluded (no displacement interactions are expected).

#### Interactions potentially affecting the efficacy of sugammadex (displacement interactions):

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

#### Toremifene:

For toremifene, which has a relatively high binding affinity for sugammadex and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with sugammadex could occur. Clinicians should be aware that 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. 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. For re-administration of sugammadex see SmPC, section 4.2.

#### Interactions potentially affecting the efficacy of other medicinal products (capturing interactions):

Due to the administration of sugammadex, certain medicinal products could become less effective due to a lowering of the (free) plasma concentrations. If such a situation is observed, the clinician is advised to consider the re-administration of the medicinal product, the administration of a therapeutically equivalent medicinal product (preferably from a different chemical class) and/or non-pharmacological interventions as appropriate.

#### Hormonal contraceptives:

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

hormonal contraceptive method for the next 7 days and refer to the advice in the package leaflet of the product.

#### Interactions due to the lasting effect of rocuronium or vecuronium:

When medicinal products which potentiate neuromuscular blockade are used in the post-operative period special attention should be paid to the possibility of recurrence of neuromuscular blockade. Please refer to the package leaflet of rocuronium or vecuronium for a list of the specific medicinal products which potentiate neuromuscular blockade. In case recurrence of neuromuscular blockade is observed, the patient may require mechanical ventilation and re-administration of sugammadex (see SmPC, section 4.2).

### **Fertility, pregnancy and lactation**

#### Pregnancy

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

#### Breast-feeding

It is unknown whether sugammadex is excreted in human breast milk. Animal studies have shown excretion of sugammadex in breast milk. Oral absorption of cyclodextrins in general is low and no effect on the suckling child is anticipated following a single dose to the breast-feeding woman. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from sugammadex therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

#### Fertility

The effects with sugammadex on human fertility have not been investigated. Animal studies to evaluate fertility do not reveal harmful effects.

### **Undesirable effects**

#### Summary of the safety profile

Bridion is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess. The most commonly reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication (Common ( $\geq 1/100$  to  $< 1/10$ )).

**Table 2: Tabulated list of adverse reactions**

The safety of sugammadex has been evaluated in 3,519 unique subjects across a pooled phase I-III safety database. The following adverse reactions were reported in placebo controlled trials where subjects received anaesthesia and/or neuromuscular blocking agents (1,078 subject exposures to sugammadex versus 544 to placebo):

*[Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ ), rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ ), very rare ( $< 1/10\ 000$ )]*

System organ class	Frequencies	Adverse reactions (Preferred terms)
Immune system disorders	Uncommon	Drug hypersensitivity reactions (see SmPC, section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Cough
Injury, poisoning and procedural complications	Common	Airway complication of anaesthesia  Anaesthetic complication (see SmPC, section 4.4)  Procedural hypotension  Procedural complication

#### Description of selected adverse reactions

##### Drug hypersensitivity reactions:

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

These reactions varied from isolated skin reactions to serious systemic reactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to sugammadex.

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

##### Airway complication of anaesthesia:

Airway complications of anaesthesia included bucking against the endotracheal tube, coughing, mild bucking, arousal reaction during surgery, coughing during the anaesthetic procedure or during surgery, or anaesthetic procedure-related spontaneous breath of patient.

##### Anaesthetic complication:

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 suckling on the endotracheal tube. See SmPC, section 4.4 light anaesthesia.

##### Procedural complication:

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

##### Marked bradycardia:

In post-marketing, isolated cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex (see SmPC, section 4.4).

#### Recurrence of neuromuscular blockade:

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labelled for the depth of neuromuscular blockade (N=2,022), an incidence of 0.20% was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence (see SmPC, section 4.4).

#### Information on healthy volunteers:

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

In a previous study of similar design, there were three adjudicated cases of anaphylaxis, all after sugammadex 16 mg/kg (incidence 2.0%).

In the Pooled Phase 1 database, AEs considered common ( $\geq 1/100$  to  $< 1/10$ ) or very common ( $\geq 1/10$ ) and more frequent among subjects treated with sugammadex than in the placebo group, include dysgeusia (10.1%), headache (6.7%), nausea (5.6%), urticaria (1.7%), pruritus (1.7%), dizziness (1.6%), vomiting (1.2%) and abdominal pain (1.0%).

#### *Additional information on special populations*

##### Pulmonary patients:

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

##### *Paediatric population*

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

##### *Morbidly obese patients*

In one dedicated clinical trial in morbidly obese patients, the safety profile was generally similar to the profile in adult patients in pooled Phase 1 to 3 studies (see Table 2).

##### *Patients with severe systemic disease*

In a trial in patients who were assessed as American Society of Anesthesiologists (ASA) Class 3 or 4 (patients with severe systemic disease or patients with severe systemic disease that is a constant threat to life), the adverse reaction profile in these ASA Class 3 and 4 patients was generally similar to that of adult patients in pooled Phase 1 to 3 studies (see Table 2). see SmPC, section 5.1.

#### **Overdose**

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

## **List of excipients**

Hydrochloric acid 3.7% (to adjust pH) and/or sodium hydroxide (to adjust pH)  
Water for injections

## **Shelf life**

3 years

After first opening and dilution chemical and physical in-use stability has been demonstrated for 48 hours at 2 °C 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 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

## **Special precautions for storage**

Store below 30 °C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see SmPC, section 6.3.

## **Special precautions for disposal and other handling**

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%), Ringers lactate solution, Ringers solution, glucose 50 mg/mL (5%) in sodium chloride 9 mg/mL (0.9%).

The infusion line should be adequately flushed (e.g., with 0.9% sodium chloride) between administration of Bridion and other drugs.

### Use in the paediatric population

For paediatric patients Bridion can be diluted using sodium chloride 9 mg/mL (0.9%) to a concentration of 10 mg/mL (see SmPC, section 6.3).

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II-016