Selected Safety Information

Bridion 100 mg/mL solution for injection

Qualitative and quantitative composition

- 1 mL 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.

Therapeutic indications

- 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 children and adolescents aged 2 to 17 years.

Contraindications

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

Special warnings and precautions for use

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 postoperative 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.
Effect on haemostasis:
Based on the clinical data-base (N=3,519) and on a specific study in 1184 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 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 comorbid condition.
Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg sugammadex):
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 readministration of rocuronium 1.2 mg/kg within 30 minutes after sugammadex administration.
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.
Renal impairment:
Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis.

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. 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.
Hepatic impairment:
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.
Delayed recovery:
Conditions associated with prolonged circulation time such as cardiovascular disease, old age, 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.
Patients on a controlled sodium diet:
Each mL solution contains up to 9.7 mg sodium. A dose of 23 mg sodium is considered essentially ‘sodium-free’. If more than 2.4 mL solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet.

Adverse Events

Drug hypersensitivity reactions:
Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers. 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.
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.

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.

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

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

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.

Drugs Interactions

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 T4/T1 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 T4/T1 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.

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

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.

Interference with laboratory tests:

In general sugammadex does not interfere with laboratory tests, with the possible exception of the serum progesterone assay. 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.

Paediatric population

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

Posology and method of administration

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.

The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed.

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

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 T4/T1 ratio to 0.9 is around 3 minutes.
- A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T4/T1 ratio to 0.9 is around 2 minutes.
- Using the recommended doses for routine reversal will result in a slightly faster median time to recovery of the T4/T1 ratio to 0.9 of rocuronium when compared to vecuronium induced neuromuscular blockade.

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 T4/T1 ratio to 0.9 of approximately 1.5 minutes can be expected.

Additional information on special population

Renal impairment:

The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis (CrCl < 30 mL/min)) is not recommended. For mild and moderate renal impairment (creatinine clearance ≥ 30 and < 80 mL/min): the dose recommendations are the same as for adults without renal impairment.

Elderly patients:

After administration of sugammadex at reappearance of T2 following a rocuronium induced blockade, the median time to recovery of the T4/T1 ratio to 0.9 in adults (18-64 years) was 2.2 minutes, in elderly adults (65-74 years) it was 2.6 minutes and in very elderly adults (75 years or more) it was 3.6 minutes. Even though the recovery times in elderly tend to be slower, the same dose recommendation as for adults should be followed.

Obese patients:

In obese patients, the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed.

Hepatic impairment:

Caution should be exercised when considering the use of sugammadex in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy. For mild to moderate hepatic impairment: as sugammadex is mainly excreted renally no dose adjustments are required.

Paediatric population

Children and adolescents:

- For routine reversal of rocuronium induced blockade at reappearance of T2 in children and adolescents (2-17 years) 2 mg/kg sugammadex is recommended. Other routine reversal situations have not been investigated and are therefore not recommended until further data become available.
- Immediate reversal in children and adolescents has not been investigated and is therefore not recommended until further data become available.

Term newborn infants and infants:

There is only limited experience with the use of sugammadex in infants (30 days to 2 years), and term newborn infants (less than 30 days) have not been studied. The use of sugammadex in term newborn infants and infants is therefore not recommended until further data become available.

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

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.

Method of administration

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

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