

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bridion 100 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains sugammadex sodium equivalent to 100 mg sugammadex.
2 ml contains sugammadex sodium equivalent to 200 mg sugammadex.
5 ml contains sugammadex sodium equivalent to 500 mg sugammadex.

For a full list of excipients, see section 6.1.

Excipient(s):

Each ml contains 9.7 mg sodium (see section 4.4).

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless to slightly yellow solution.

The pH is between 7 and 8 and osmolality is between 300 and 500 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reversal of neuromuscular blockade induced by rocuronium or vecuronium.

For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents.

4.2 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. 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 re-occurrence of blockade (see section 4.4). When certain medicinal products that may cause displacement interactions are administered parenterally within a period of 6 hours of sugammadex, the patient should be monitored for signs of re-occurrence of blockade (see section 4.4 and 4.5).

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

The recommended dose does not depend on the anaesthetic regimen.

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 T_4/T_1 ratio to 0.9 is around 3 minutes (see 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 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 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 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 re-occurrence of blockade post-operatively (see 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.

Re-administration of rocuronium or vecuronium after sugammadex:

A waiting time of 24 hours should be taken into account (see section 4.4).

Additional information on special population

Renal impairment:

For mild and moderate renal impairment (creatinine clearance ≥ 30 and < 80 ml/min): the dose recommendations are the same as for adults.

The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis (CrCl < 30 ml/min)) is not recommended (see section 4.4).

Elderly patients:

After administration of sugammadex at reappearance of T_2 following a rocuronium induced blockade, the median time to recovery of the T_4/T_1 ratio to 0.9 in adults (18-64 years) was 2.2 minutes, in elderly adults (65-74 years) it was 2.6 minutes and in very elderly adults (75 years or more) it was 3.6 minutes. Even though the recovery times in elderly tend to be slower, the same dose recommendation as for adults should be followed (see section 4.4).

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:

For mild to moderate hepatic impairment: as sugammadex is mainly excreted renally no dose adjustments are required.

Studies in patients with hepatic impairment have not been conducted and therefore patients with severe hepatic impairment should be treated with great caution (see section 4.4).

Paediatric population:

The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T_2).

Children and adolescents:

For **routine** reversal of rocuronium induced blockade at reappearance of T_2 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.

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

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.

Method of administration

Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds directly into a vein or into an existing intravenous line (see section 6.6). Sugammadex has only been administered as a single bolus injection in clinical trials.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 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 block. 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.

Re-occurrence of blockade:

In clinical trials re-occurrence of blockade was reported mainly when sub-optimal doses (in dose finding studies) were administered. In order to prevent re-occurrence of neuromuscular blockade, the recommended doses for routine or immediate reversal (see section 4.2) should be used.

Effect on hemostasis:

In a study in volunteers doses of 4 mg/kg and 16 mg/kg of sugammadex prolonged by 17-22% the activated partial thromboplastin time (aPTT) and prothrombin time (PT). In all cases, this slight prolongation was of short duration (< than 30 minutes). Based on the clinical data-base (n=1738) there was no clinically relevant effect of sugammadex 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 can not 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 hemostasis and coagulation parameters is recommended.

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

If re-administration of rocuronium or vecuronium is required a waiting time of 24 hours is recommended.

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

Renal impairment:

In patients with severe renal failure (creatinine clearance < 30 ml/min) the excretion of sugammadex or the sugammadex-rocuronium complex was delayed, however in these patients there were no signs of re-occurrence of neuromuscular blockade. Data from a limited number of renally impaired patients requiring dialysis indicate an inconsistent decrease of plasma levels of sugammadex by haemodialysis. The use of sugammadex in patients with severe renal impairment is not recommended.

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 re-occurrence of 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 re-occurrence of blockade is observed, the patient may require mechanical ventilation and re-administration of sugammadex (see section 4.2).

Potential interactions:

- **Capturing interactions:**
Due to the administration of sugammadex, certain medicinal products could become less effective due to a lowering of the (free) plasma concentrations (see section 4.5, hormonal contraceptives).
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.
- **Displacement interactions:**
Due to the administration of certain medicinal products after sugammadex, theoretically rocuronium or vecuronium could be displaced from sugammadex. As a result re-occurrence of blockade might be observed. In this situation the patient must be ventilated. Administration of the medicinal product which caused displacement should be stopped in case of an infusion. In situations when potential displacement interactions can be anticipated, patients should be carefully monitored for signs of re-occurrence of blockade (approximately up to 15 minutes) after parenteral administration of another medicinal product occurring within a period of 6 hours after sugammadex administration. Displacement interactions are at present only expected for a few drugs substances (toremifene and fusidic acid, see section 4.5).

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.

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.

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 section 4.2 for the time to recovery in elderly), or oedematous state 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 section 4.8).

Patients on a controlled sodium diet:

Each ml solution contains 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.

QTc-interval prolongation:

Two thorough QTc trials (N=146), both in conscious volunteers, demonstrated that sugammadex alone or in combination with rocuronium or vecuronium is not associated with QTc interval prolongation. The one-sided 95% upper confidence limits for the QTc difference to placebo were well below the 10 ms margin for each of the 12-13 evaluated timepoints in both studies.

In the clinical program, a few cases of QTc prolongation were reported (QTc > 500 msec or QTc increases > 60 msec) in clinical trials in which patients received sugammadex in combination with sevoflurane or propofol. During anaesthesia several medicinal products with the potential to prolong QTc (e.g. sevoflurane) are administered. The routine precautions for treating arrhythmia should be taken into consideration.

4.5 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 (see also section 4.4):

Toremifene:

For toremifene, which has a relatively high affinity constant and relatively high plasma concentrations, some displacement of vecuronium or rocuronium from the complex with sugammadex could occur. 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 re-occurrence of neuromuscular blockade is expected in the post-operative phase,

since the infusion rate of fucidic acid is over a period of several hours and the blood levels are cumulative over 2-3 days. For re-administration of sugammadex see section 4.2.

Interactions potentially affecting the efficacy of other medicinal products (see also section 4.4):

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 missed daily dose of an oral contraceptive is taken 12 hours too late, which might lead to a reduction in effectiveness. For estrogens, 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. Interference with this test is observed at sugammadex plasma concentrations of 100 µg/ml (peak plasma level following 8 mg/kg bolus injection).

In a study in volunteers doses of 4 mg/kg and 16 mg/kg of sugammadex prolonged by 17-22% the activated partial thromboplastin time (aPTT) and prothrombin time (PT). In all cases, this slight prolongation was of short duration (< than 30 minutes).

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 (see section 4.4).

Paediatric population

No formal interaction studies have been performed. The above mentioned interactions for adults and the warnings in section 4.4 should also be taken into account for the paediatric population.

4.6 Pregnancy and lactation

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.

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 effects on the suckling child is anticipated following a single dose to the breast-feeding woman. Sugammadex can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of sugammadex has been evaluated based on an integrated safety database of approximately 1700 patients and 120 volunteers. The most commonly reported adverse reaction dysgeusia (metal or bitter taste) was mainly seen after doses of 32 mg/kg sugammadex or higher.

Body system	Subject incidence	Undesirable effect
Immune system disorders	Uncommon ($\geq 1/1000$ to $< 1/100$)	Drug hypersensitivity reactions (see section 4.4)
Injury, poisoning and procedural complications	Common ($\geq 1/100$ to $< 1/10$)	Anaesthetic complication (see section 4.4)
	Uncommon ($\geq 1/1000$ to $< 1/100$)	Unwanted awareness during anaesthesia
Nervous system disorders	Very common ($\geq 1/10$) in volunteers	Dysgeusia

Drug hypersensitivity reactions:

Hypersensitivity reactions have occurred in some patients and volunteers. In clinical trials these reactions were reported uncommonly and for post-marketing reports the frequency is unknown. These reactions varied from isolated skin reactions to serious systemic reactions (i.e. anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to sugammadex. Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia and swelling of tongue and pharynx.

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 section 4.4 light anaesthesia.

Awareness:

In sugammadex treated subjects a few cases of awareness were reported. The relation to sugammadex is uncertain.

Re-occurrence of blockade:

In the data-base of pooled phase I-III studies with a placebo group, the incidence of re-occurrence of blockade as measured with neuromuscular monitoring was 2% after sugammadex and 0% in the placebo group. Virtually all of these cases were from dose-finding studies in which a sub-optimal dose (less than 2 mg/kg) was administered (see section 4.4).

Additional information on special populations

Pulmonary patients:

In one clinical trial in patients with a history of pulmonary complications bronchospasm was reported as a possibly related adverse event in two patients and a causal relationship could not be fully excluded. 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.

4.9 Overdose

In clinical studies, 1 case of an accidental overdose with 40 mg/kg was reported without any significant undesirable effects. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: all other therapeutic products, ATC code: V03AB35

Mechanism of action:

Sugammadex is a modified gamma cyclodextrin which is a Selective Relaxant Binding Agent. It forms a complex with the neuromuscular blocking agents rocuronium or vecuronium in plasma and 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.

Pharmacodynamic effects:

Sugammadex has been administered in doses ranging from 0.5 mg/kg to 16 mg/kg in dose response studies of rocuronium induced blockade (0.6, 0.9, 1.0 and 1.2 mg/kg rocuronium bromide with and without maintenance doses) and vecuronium induced blockade (0.1 mg/kg vecuronium bromide with or without maintenance doses) at different time points/depths of blockade. In these studies a clear dose-response relationship was observed.

Clinical efficacy and safety:

Sugammadex can be administered at several time points after administration of rocuronium or vecuronium bromide:

Routine reversal – deep neuromuscular blockade:

In a pivotal study patients were randomly assigned to the rocuronium or vecuronium group. After the last dose of rocuronium or vecuronium, at 1-2 PTCs, 4 mg/kg sugammadex or 70 mcg/kg neostigmine was administered in a randomised order. The time from start of administration of sugammadex or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was:

Time (minutes) from administration of sugammadex 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	
	Sugammadex (4 mg/kg)	Neostigmine (70 mcg/kg)
Rocuronium		
N	37	37
Median (minutes)	2.7	49.0
Range	1.2-16.1	13.3-145.7
Vecuronium		
N	47	36
Median (minutes)	3.3	49.9
Range	1.4-68.4	46.0-312.7

Routine reversal – moderate neuromuscular blockade:

In another pivotal study 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 mg/kg sugammadex or 50 mcg/kg neostigmine was administered in a randomised order. The time from start of administration of sugammadex or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was:

Time (minutes) from administration of sugammadex or neostigmine at reappearance of T_2 after rocuronium or vecuronium to recovery of the T_4/T_1 ratio to 0.9

Neuromuscular blocking agent	Treatment regimen	
	Sugammadex (2 mg/kg)	Neostigmine (50 mcg/kg)
Rocuronium		
N	48	48
Median (minutes)	1.4	17.6
Range	0.9-5.4	3.7-106.9

Vecuronium		
N	48	45
Median (minutes)	2.1	18.9
Range	1.2-64.2	2.9-76.2

Reversal by sugammadex of the neuromuscular blockade induced by rocuronium was compared to the reversal by neostigmine of the neuromuscular blockade induced by cis-atracurium. At the reappearance of T₂ a dose of 2 mg/kg sugammadex or 50 mcg/kg neostigmine was administered. Sugammadex provided faster reversal of neuromuscular blockade induced by rocuronium compared to neostigmine reversal of neuromuscular blockade induced by cis-atracurium:

Time (minutes) from administration of sugammadex or neostigmine at reappearance of T₂ after rocuronium or cis-atracurium to recovery of the T₄/T₁ ratio to 0.9

Neuromuscular blocking agent	Treatment regimen	
	Rocuronium and sugammadex (2 mg/kg)	Cis-atracurium and neostigmine (50 mcg/kg)
N	34	39
Median (minutes)	1.9	7.2
Range	0.7-6.4	4.2-28.2

For immediate reversal:

The time to recovery from succinylcholine-induced neuromuscular blockade (1 mg/kg) was compared with sugammadex (16 mg/kg, 3 minutes later) – induced recovery from rocuronium-induced neuromuscular blockade (1.2 mg/kg).

Time (minutes) from administration of rocuronium and sugammadex or succinylcholine to recovery of the T₁ 10%

Neuromuscular blocking agent	Treatment regimen	
	Rocuronium and sugammadex (16 mg/kg)	Succinylcholine (1 mg/kg)
N	55	55
Median (minutes)	4.2	7.1
Range	3.5-7.7	3.7-10.5

In a pooled analysis the following recovery times for 16 mg/kg sugammadex after 1.2 mg/kg rocuronium bromide were reported:

Time (minutes) from administration of sugammadex at 3 minutes after rocuronium to recovery of the T₄/T₁ ratio to 0.9, 0.8 or 0.7

	T ₄ /T ₁ to 0.9	T ₄ /T ₁ to 0.8	T ₄ /T ₁ to 0.7
N	65	65	65
Median (minutes)	1.5	1.3	1.1
Range	0.5-14.3	0.5-6.2	0.5-3.3

5.2 Pharmacokinetic properties

The sugammadex pharmacokinetic parameters were calculated from the total sum of non-complex-bound and complex-bound concentrations of sugammadex. Pharmacokinetic parameters as clearance and volume of distribution are assumed to be the same for non-complex-bound and complex-bound sugammadex in anaesthetised subjects.

Distribution:

The steady-state volume of distribution of sugammadex is approximately 11 to 14 litres. Neither sugammadex nor the complex of sugammadex and rocuronium bind to plasma proteins or

erythrocytes, as was shown in vitro using male human plasma and whole blood. 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.

Elimination:

The elimination half-life ($t_{1/2}$) of sugammadex in adults is 1.8 hours and plasma clearance is estimated to be 88 ml/min. A mass balance study demonstrated that > 90% of the dose was excreted within 24 hours. 96% of the dose was excreted in urine, of which at least 95% could be attributed to unchanged sugammadex. Excretion via faeces or expired air was less than 0.02% of the dose. Administration of sugammadex to healthy volunteers resulted in increased renal elimination of rocuronium in complex.

Special populations:

Elderly and renal impairment:

The pharmacokinetic parameters based on pharmacokinetic modelling in typical elderly and/or renally impaired patients are presented below:

Typical subject (75 kg body weight)		Clearance (ml/min)	Volume of Distribution at Steady State (l)	Elimination half-life (h)
Adult (40 years)	Normal CrCL: 100 ml/min	88 (25.0%)	11.4 (22.9%)	1.8 (32.9%)
Adult (40 years)	Mild renal impairment CrCL: 50 ml/min	71 (23.6%)	11.4 (23.0%)	2.2 (33.3%)
Adult (40 years)	Moderate renal impairment CrCL: 30 ml/min	28 (24.4%)	11.4 (23.5%)	5.2 (32.9%)
Elderly (75 years)	Normal CrCL: 80 ml/min	80 (24.0%)	13.5 (24.4%)	2.4 (34.9%)
Elderly (75 years)	Mild renal impairment CrCL: 50 ml/min	72 (24.5%)	13.2 (24.2%)	2.6 (34.6%)
Elderly (75 years)	Moderate renal impairment CrCL: 30 ml/min	28 (24.7%)	13.4 (23.8%)	6.1 (36.5%)

Mean and CV (%) are presented.

Paediatrics:

Pharmacokinetics in paediatric patients (n=51) with ages ranging from 0 to 17 years were evaluated using population pharmacokinetic (PK) analysis. In patients under age 18, volume of distribution and clearance increase with increasing age. Variability of plasma concentrations of sugammadex in paediatric patients is comparable to the variability in adult patients. The pharmacokinetic (PK) parameters of two typical paediatric patients are summarised below:

PK Parameters of sugammadex in typical paediatric patients		
PK Parameter	Child (Age:8 yr)	Adolescent (Age: 15 yr)
Elimination Half-Life (h)	0.9	1.7
Volume of Distribution at Steady State (l)	3.1	9.1
Clearance (ml/min)	41	71

Gender:

No gender differences were observed.

Race:

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

Body weight:

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

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity potential, and toxicity to reproduction, local tolerance or compatibility with blood.

Sugammadex is rapidly cleared from most organs; however some retention of compound occurs in bone and teeth in the rat. The most likely component involved in the reversible binding is hydroxy apatite, the inorganic matrix in these tissues. Preclinical studies in young adult and mature rats have shown that this retention does not adversely affect tooth colour or bone quality, structure, turnover and development. In juvenile rats whitish discoloration was observed in the incisors and disturbance of enamel formation was observed upon repeated dosing, however at exposure levels of 48-480 times the clinical exposure at 4 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Physical incompatibility has been reported with verapamil, ondansetron and ranitidine.

6.3 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.

6.4 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 section 6.3.

6.5 Nature and contents of container

Single use type I glass vial closed with grey chlorobutyl rubber stoppers with aluminium crimp-cap and flip-off seal.

The rubber stopper of the vial does not contain latex.

Pack sizes: 10 vials of 2 ml or 10 vials of 5 ml.
Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

If Bridion is administered via the same infusion line that is also used for other medicinal products, it is important that the infusion line is adequately flushed (e.g. with sodium chloride 9 mg/ml (0.9% solution)) between administration of Bridion and medicinal products for which incompatibility with Bridion has been demonstrated or for which compatibility with Bridion has not been established.

Sugammadex 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 (see section 6.3).

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

7. MARKETING AUTHORISATION HOLDER

N.V. Organon, Kloosterstraat 6, 5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/466/001

EU/1/08/466/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 July 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDERS
RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

N.V. Organon
Kloosterstraat 6
P.O. Box 20
NL-5340 BH Oss
The Netherlands

Organon (Ireland) Ltd
Drynam Road
Swords Co.
Dublin
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 7.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.1 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, 10 x 5 ml vials

1. NAME OF THE MEDICINAL PRODUCT

Bridion 100 mg/ml solution for injection
sugammadex

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 mg sugammadex (as sodium salt).
5 ml = 500 mg

3. LIST OF EXCIPIENTS

Other ingredients: hydrochloric acid 3.7% and/or sodium hydroxide (to adjust pH), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV
Intravenous use.
For single use only.
Discard any unused solution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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 2-8°C and use within 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/466/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL, 10 x 5 ml vials

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bridion 100 mg/ml injection
sugammadex
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON, 10 x 2 ml vials

1. NAME OF THE MEDICINAL PRODUCT

Bridion 100 mg/ml solution for injection
sugammadex

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 mg sugammadex (as sodium salt).
2 ml = 200 mg

3. LIST OF EXCIPIENTS

Other ingredients: hydrochloric acid 3.7% and/or sodium hydroxide (to adjust pH), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

IV
Intravenous use.
For single use only.
Discard any unused solution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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 2-8°C and use within 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/466/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL, 10 x 2 ml vials

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Bridion 100 mg/ml injection
sugammadex
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

B. PACKAGE LEAFLET

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.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your anaesthetist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your anaesthetist or other doctor.

In this leaflet:

1. What Bridion is and what it is used for
2. Before Bridion is given
3. How Bridion is given
4. Possible side effects
5. How Bridion is stored
6. Further information

1. WHAT BRIDION IS AND WHAT IT IS USED FOR

Bridion is one of a group of medicines called *Selective Relaxant Binding Agents*. It is used to speed up the recovery of your muscles after an operation.

When you have some types of operation, 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 stop muscle relaxants working. It does this by combining with the rocuronium bromide or vecuronium bromide in your body. Bridion is given to speed up your recovery from the muscle relaxant – for example, at the end of an operation to allow you to breathe normally earlier.

2. BEFORE BRIDION IS GIVEN

You should not be given Bridion

- if you are allergic (*hypersensitive*) to sugammadex or any of the other ingredients.
- Tell your anaesthetist if this applies to you.

Take special care with Bridion

- 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 heart disease or have had it in the past.
- if you have liver disease or have had it in the past.
- if you have fluid retention (oedema).
- if you are on a controlled salt diet.
- if you have diseases which are known to give an increased risk of bleeding (disturbances of blood clotting) or anticoagulation medication.

→ Tell your anaesthetist if any of the above applies to you.

Taking other medicines

→ Please tell your anaesthetist if you are taking or have recently taken other medicines, including medicines obtained without a prescription or herbal products.
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.

Pregnancy and breast-feeding

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

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

Sugammadex can be used during breast-feeding.

Driving and using machines

Your doctor will tell you when it is safe to drive or operate machinery after you have been given Bridion. Bridion is not known to have an effect on alertness or concentration.

3. HOW BRIDION IS GIVEN

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. A higher dose may be given if the anaesthetist wants you to recover faster.

The dose of Bridion for children is 2 mg/kg (children and adolescents between 2-17 years old).

How Bridion is given

Bridion will be given to you by your anaesthetist. It is given into a vein (intravenously) as a single injection.

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 medicinal product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Very common side effects (in more than 1 user in 10)

- A temporary unpleasant taste in your mouth.

Common side effects (in 1 to 10 users in 100)

- 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.
- Your muscles may turn weak again after the operation (if a too low dose is administered).

Uncommon side effects (in 1 to 10 users in 1,000)

- Being awake during the operation (anaesthesia awareness)
- Shortness of breath due to muscle cramps of the airways (bronchospasm) occurred in patients with a history of asthma
- Allergic (drug hypersensitivity) reactions - such as a rash, red skin, swelling of your tongue and/or throat, changes in blood pressure or heart rate, sometimes resulting in a serious decrease of blood pressure.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW BRIDION IS STORED

Keep out of the reach and sight of children.

Do not use Bridion after the expiry date which is stated on the vial and the carton.

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.

6. FURTHER INFORMATION

What Bridion contains

- The active substance is sugammadex.
1 ml solution for injection contains 100 mg sugammadex (as sodium salt)
- The other ingredients are water for injections, hydrochloric acid 3.7% and/or sodium hydroxide (to adjust pH).

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

N.V. Organon, Kloosterstraat 6, 5349 AB Oss, The Netherlands

Manufacturers

- N.V. Organon, Kloosterstraat 6, 5349 AB Oss, The Netherlands
- Organon (Ireland) Ltd., Drynam Road, Swords, Co. Dublin, Ireland

This leaflet was last approved in {MM/YYYY}

**Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>**

The following information is intended for medical or healthcare professionals only:
For detailed information refer to the Summary of Product Characteristics of BRIDION.