Package leaflet: Information for the user
Sugammadex 100mg/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 any 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 Sugammadex is and what it is used for

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

What Sugammadex 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.
Sugammadex 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 and in children and adolescents (aged 2 to 17 years) when rocuronium bromide is used for a moderate level of relaxation.

2. What you need to know before Sugammadex is given

You should not be given Sugammadex
- 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 Sugammadex is given
- if you have kidney disease or had it in the past. This is important as Sugammadex 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.

Children and adolescents
This medicine is not recommended for infants less than 2 years of age.

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

Some medicines reduce the effect of Sugammadex
→ It is especially important that you tell your anaesthetist if you have recently taken:
- toremifene (used to treat breast cancer).
- fusidic acid (an antibiotic).

Sugammadex can affect hormonal contraceptives
- Sugammadex 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 Sugammadex is about the same as missing one oral contraceptive Pill.
  → If you are taking the **Pill** on the same day as Sugammadex 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, Sugammadex 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 Sugammadex.

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 Sugammadex, 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 Sugammadex to the mother.

Driving and using machines
Sugammadex has no known influence on your ability to drive and use machines.

Sugammadex injection contains sodium
This medicine contains up to 9.7mg 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 Sugammadex is given

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

The following information is intended for healthcare professionals only:
For detailed information refer to the Summary of Product Characteristics of Sugammadex 100mg/ml Solution for Injection.

Sugammadex 100mg/ml Solution for Injection
sugammadex
Information for the doctor

1. NAME OF THE MEDICINAL PRODUCT

Sugammadex 100mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
The total amount of sodium in each ml is up to 9.7mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear solution, colourless to slightly yellow-brown, free from visible particles.
The pH is between 7 and 8 and osmolality is between 300 and 500mOsm/kg.

4. CLINICAL PARTICULARS

4.1 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.

4.2 Posology and method of administration

Posology
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 section 4.4).
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 4mg/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 2mg/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 16mg/kg sugammadex is recommended. When 16mg/kg sugammadex is administered 3 minutes after a bolus dose of 1.2mg/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 recurrence of neuromuscular blockade post-operatively (see section 4.4) after an initial dose of 2mg/kg or 4mg/kg sugammadex, a repeat dose of 4mg/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:
For waiting times for re-administration of rocuronium or vecuronium after reversal with sugammadex, see section 4.4.

Additional information on special population

Renal impairment:
The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis (CrCl <30ml/min)) is not recommended (see section 4.4). Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of sugammadex in these patients (see also section 5.1).
For mild and moderate renal impairment (creatinine clearance ≥30 and <80ml/min): the dose recommendations are the same as for adults without renal impairment.

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, including morbidly obese patients (body mass index ≥40kg/m²), the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed.

Hepatic impairment:
Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of sugammadex in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see section 4.4).
For mild to moderate hepatic impairment: as sugammadex is mainly excreted renally no dose adjustments are required.

Paediatric population

Children and adolescents (2-17 years):
Sugammadex 100mg/ml may be diluted to 10mg/ml to increase the accuracy of dosing in the paediatric population (see section 6.6).

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

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

Immediate reversal:
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.

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 (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 listed in section 6.1.

4.4 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 section 4.2 and section 4.8).

Effect on haemostasis:
In a study in volunteers doses of 4mg/kg and 16mg/kg of sugammadex resulted in maximum mean prolongations of the activated partial thromboplastin time (aPTT) by 17 and 22% respectively and prothrombin time international normalized ratio [PT(INR)] by 11 and 22% respectively. These limited mean aPTT and PT(INR) prolongations were of short duration (≤30 minutes). 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 4mg/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 peri-operative 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 derivates and at an INR above 3.5;
- using anticoagulants who receive a dose of 16mg/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 4mg/kg sugammadex):

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

Re-administration of rocuronium or vecuronium after immediate reversal (16mg/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 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 section 4.8.) 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:
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 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 section 4.8).

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

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 (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 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 nonpharmacological interventions as appropriate.

Hormonal contraceptives:
The interaction between 4mg/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 section 4.2).

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 100microgram/ml (peak plasma level following 8mg/kg bolus injection).
In a study in volunteers doses of 4mg/kg and 16mg/kg of sugammadex resulted in maximum mean prolongations of aPTT by 17 and 22% respectively and of PT(INR) by 11 and 22% respectively.
These limited mean aPTT and PT(INR) prolongations were of short duration (≤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 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.

4.7 Effects on ability to drive and use machines
Sugammadex has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the adverse reaction profile
Sugammadex 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 (≥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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000)]

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Sugammadex 100mg/ml Solution for Injection

sugammadex

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The dose
Your anaesthetist will work out the dose of Sugammadex you need based on:
- your weight
- how much the muscle relaxant medicine is still affecting you.

The usual dose is 2-4mg per kg body weight for adults and for children and adolescents between 2-17 years old. A dose of 16mg/kg can be used in adults if urgent recovery from muscle relaxation is needed.

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

If more Sugammadex 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 Sugammadex. 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 Sugammadex 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 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 Sugammadex

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.
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 protected from light and use within 24 hours.

6. Contents of the pack and other information

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

What Sugammadex looks like and contents of the pack
Sugammadex is a clear and colourless to slightly yellow-brown solution for injection.
It comes in two different pack sizes, containing either 10 vials with 2ml or 10 vials with 5ml solution for injection.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Wockhardt UK Ltd.
Ash Road North, Wrexham, LL13 9UF, UK

Manufacturer
PLIVA Hrvatska d.o.o. (PLIVA Croatia Ltd.)
Prilaz baruna Filipovića 25
Zagreb 10000
Croatia

Other formats:
To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: 0800 198 5000.
Please be ready to give the following information:

Product Name	Reference Number
Sugammadex 100mg/ml Solution for Injection	29831/0767

This is a service provided by the Royal National Institute of Blind People.

This leaflet was last revised in 09/2023.

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System organ class	Frequencies	Adverse reactions (preferred terms)
Immune system disorders	Uncommon	Drug hypersensitivity reactions (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Common	Cough
Injury, poisoning and procedural complications	Common	Airway complication of anaesthesia Anaesthetic complication (see 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 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 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 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 4mg/kg (N=151) or sugammadex 16mg/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 4mg/kg and sugammadex 16mg/kg groups, respectively. There were no reports of anaphylaxis after placebo or sugammadex 4mg/kg. There was a single case of adjudicated anaphylaxis after the first dose of sugammadex 16mg/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 16mg/kg (incidence 2.0%).
In the Pooled Phase 1 database, AEs considered common (≥1/100 to <1/10) or very common (≥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 2 to 17 years of age, the adverse reaction profile of sugammadex (up to 4mg/kg) was generally similar to the profile observed in adults.

Morbidly obese patients

In one dedicated clinical trial in morbidly obese patients, the adverse reaction 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 section 5.1.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
In clinical studies, 1 case of an accidental overdose with 40mg/kg was reported without any significant adverse reactions. In a human tolerance study sugammadex was administered in doses up to 96mg/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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: all other therapeutic products, antidotes, 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 0.5mg/kg to 16mg/kg in dose response studies of rocuronium induced blockade (0.6, 0.9, 1.0 and 1.2mg/kg rocuronium bromide with and without maintenance doses) and vecuronium induced blockade (0.1mg/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, 4mg/kg sugammadex or 70mcg/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:

Table 3: 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 (4mg/kg)	Neostigmine (70mcg/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, 2mg/kg sugammadex or 50mcg/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:

Table 4: 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 (2mg/kg)	Neostigmine (50mcg/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 T_2 a dose of 2mg/kg sugammadex or 50mcg/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:

Table 5: Time (minutes) from administration of sugammadex or neostigmine at reappearance of T_2 after rocuronium or cis-atracurium to recovery of the T_4/T_1 ratio to 0.9

Neuromuscular blocking agent	Treatment regimen	
	Rocuronium and sugammadex (2mg/kg)	Cis-atracurium and neostigmine (50mcg/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 (1mg/kg) was compared with sugammadex (16mg/kg, 3 minutes later) – induced recovery from rocuronium-induced neuromuscular blockade (1.2mg/kg).

Table 6: Time (minutes) from administration of rocuronium and sugammadex or succinylcholine to recovery of the T_1 10%

Neuromuscular blocking agent	Treatment regimen	
	Rocuronium and sugammadex (16mg/kg)	Succinylcholine (1mg/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 16mg/kg sugammadex after 1.2mg/kg rocuronium bromide were reported:

Table 7: Time (minutes) from administration of sugammadex at 3 minutes after rocuronium to recovery of the T_4/T_1 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

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

Morbidly obese patients:
A trial of 188 patients who were diagnosed as morbidly obese investigated the time to recovery from moderate or deep neuromuscular blockade induced by rocuronium or vecuronium. Patients received 2mg/kg or 4mg/kg sugammadex, as appropriate for level of block, dosed according to either actual body weight or ideal body weight in random, double-blinded fashion. Pooled across depth of block and neuromuscular blocking agent, the median time to recover to a train-of-four (TOF) ratio ≥0.9 in patients dosed by actual body weight (1.8 minutes) was statistically significantly faster (p <0.0001) compared to patients dosed by ideal body weight (3.3 minutes).

Paediatric Population:
A trial of 288 patients aged 2 to <17 years investigated the safety and efficacy of sugammadex versus neostigmine as a reversal agent for neuromuscular blockade induced by rocuronium or vecuronium. Recovery from moderate block to a TOF ratio of ≥0.9 was significantly faster in the sugammadex 2mg/kg group compared with the neostigmine group (geometric mean of 1.6 minutes for sugammadex 2mg/kg and 7.5 minutes for neostigmine, ratio of geometric means 0.22, 95% CI (0.16, 0.32), (p<0.0001)). Sugammadex 4mg/kg achieved reversal from deep block with a geometric mean of 2.0 minutes, similar to results observed in adults. These effects were consistent for all age cohorts studied (2 to <6; 6 to <12; 12 to <17 years of age) and for both rocuronium and vecuronium. See section 4.2.

Patients with severe systemic disease:
A trial of 331 patients who were assessed as ASA Class 3 or 4 investigated the incidence of treatment-emergent arrhythmias (sinus bradycardia, sinus tachycardia or other cardiac arrhythmias) after administration of sugammadex. In patients receiving sugammadex (2mg/kg, 4mg/kg, or 16mg/kg), the incidence of treatment-emergent arrhythmias was generally similar to neostigmine (50µg/kg up to 5mg maximum dose) + glycopyrrolate (10µg/kg up to 1mg maximum dose). The adverse reaction profile in ASA Class 3 and 4 patients was generally similar to that of adult patients in pooled Phase 1 to 3 studies; therefore, no dosage adjustment is necessary. See section 4.8.

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 observed steady-state volume of distribution of sugammadex is approximately 11 to 14 litres in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Neither sugammadex nor the complex of sugammadex and rocuronium binds 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 16mg/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:
In adult anaesthetized patients with normal renal function the elimination half-life ($t_{1/2}$) of sugammadex is about 2 hours and the estimated plasma clearance is about 88ml/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:

Renal impairment and age:
In a pharmacokinetic study comparing patients with severe renal impairment to patients with normal renal function, sugammadex levels in plasma were similar during the first hour after dosing, and thereafter the levels decreased faster in the control group. Total exposure to sugammadex was prolonged, leading to 17-fold higher exposure in patients with severe renal impairment. Low concentrations of sugammadex are detectable for at least 48 hours post-dose in patients with severe renal insufficiency.
In a second study comparing subjects with moderate or severe renal impairment to subjects with normal renal function, sugammadex clearance progressively decreased and $t_{1/2}$ was progressively prolonged with declining renal function. Exposure was 2-fold and 5-fold higher in subjects with moderate and severe renal impairment, respectively. Sugammadex concentrations were no longer detectable beyond 7 days post-dose in subjects with severe renal insufficiency.

Table 8: A summary of sugammadex pharmacokinetic parameters stratified by age and renal function is presented below:

Selected patient characteristics				Mean Predicted PK parameters (CV*%)		
Demographics Age Body weight	Renal function Creatinine clearance (ml/min)			Clearance (ml/min)	Volume of distribution at steady state (L)	Elimination half-life (hr)
Adult	Normal		100	84 (24)	13	2 (22)
40 years 75 kg	Impaired	Mild Moderate Severe	50 30 10	47 (25) 28 (24) 8 (25)	14 14 15	4 (22) 7 (23) 24 (25)
Elderly	Normal		80	70 (24)	13	3 (21)
75 years 75 kg	Impaired	Mild Moderate Severe	50 30 10	46 (25) 28 (25) 8 (25)	14 14 15	4 (23) 7 (23) 24 (24)
Adolescent	Normal		95	72 (25)	10	2 (21)
15 years 56 kg	Impaired	Mild Moderate Severe	48 29 10	40 (24) 24 (24) 7 (25)	11 11 11	4 (23) 6 (24) 22 (25)
Middle childhood	Normal		60	40 (24)	5	2 (22)
9 years 29 kg	Impaired	Mild Moderate Severe	30 18 6	21 (24) 12 (25) 3 (26)	6 6 6	4 (22) 7 (24) 25 (25)
Early childhood	Normal		39	24 (25)	3	2 (22)
4 years 16 kg	Impaired	Mild Moderate Severe	19 12 4	11 (25) 6 (25) 2 (25)	3 3 3	4 (23) 7 (24) 28 (26)

*CV=coefficient of variation

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.

Obesity:
In one clinical study in morbidly obese patients, sugammadex 2mg/kg and 4mg/kg was dosed according to actual body weight (n=76) or ideal body weight (n=74). Sugammadex exposure increased in a dose-dependent, linear manner following administration according to actual body weight or ideal body weight. No clinically relevant differences in pharmacokinetic parameters were observed between morbidly obese patients and the general population.

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 in preclinical species, although residual sugammadex was observed in bone and teeth of juvenile rats. Preclinical studies in young adult and mature rats demonstrate that sugammadex does not adversely affect tooth colour or bone quality, bone structure, or bone metabolism. Sugammadex has no effects on fracture repair and remodelling of bone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Hydrochloric acid (to adjust pH)
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
Sugammadex 2ml vials: 3 years
Sugammadex 5ml vials: 2 years
After first opening and dilution chemical and physical in-use stability has been demonstrated for 48 hours at 2-8°C protected from light and at 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
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
Colourless glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium cap with salmon coloured polypropylene disk.
Pack sizes: 10 vials of 2ml or 10 vials of 5ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Sugammadex can be injected into the intravenous line of a running infusion with the following intravenous solutions: sodium chloride 9mg/ml (0.9%), glucose 50mg/ml (5%), sodium chloride 4.5mg/ml (0.45%) and glucose 25mg/ml (2.5%), Ringers lactate solution, Ringers solution, glucose 50mg/ml (5%) in sodium chloride 9mg/ml (0.9%).
The infusion line should be adequately flushed (e.g., with 0.9% sodium chloride) between administration of Sugammadex and other drugs.

Use in the paediatric population
For paediatric patients Sugammadex can be diluted using sodium chloride 9mg/ml (0.9%) to a concentration of 10mg/ml (see section 6.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd.
Ash Road North, Wrexham, LL13 9UF, UK

8. MARKETING AUTHORISATION NUMBER(S)
PL 29831/0767

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/05/2023

This leaflet was last revised in 09/2023.

108724/2

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