SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TEMADEX 200, solution for injection

TEMADEX 500, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains sugammadex sodium equivalent to 100 mg sugammadex.

Each vial of 2 ml contains sugammadex sodium equivalent to 200 mg sugammadex.

Each vial of 5 ml contains sugammadex sodium equivalent to 500 mg sugammadex.

Excipient(s) with known effect

Contains up to 9,7 mg/ml sodium (see **section 4.4**).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear solution, colourless to slightly yellow-brown aqueous solution.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Routine reversal of neuromuscular blockade induced by rocuronium or vecuronium.

For the immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

For the paediatric population, TEMADEX is only recommended for routine reversal of rocuronium induced blockade in children above 7 years of age.

4.2 Posology and method of administration:

Posology:

TEMADEX 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 %) to a concentration of 10 mg/ml (see **section 6.6**).

The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of the neuromuscular blockade. When certain medicines that may cause displacement interactions are administered parenterally within 7,5 hours of TEMADEX, patients should be monitored for signs of recurrence of neuromuscular blockade.

The recommended dose of TEMADEX depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen.

TEMADEX can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade.

Routine Reversal of Neuromuscular Blockade:

A dose of 4 mg/kg TEMADEX is recommended if recovery has reached 1 to 2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade (see **section 4.4**).

A dose of 2 mg/kg TEMADEX is only recommended if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium or vecuronium induced blockade (see **section 4.4**).

Immediate Reversal:

If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16 mg/kg TEMADEX is recommended. There is no data to recommend the use of TEMADEX for immediate reversal following vecuronium induced blockade.

Special populations:

Renal impairment:

For mild and moderate renal impairment (creatinine clearance ≥ 30 and < 80 ml/min): The dose recommendations are the same as for adults without renal impairment. The use of TEMADEX in patients with severe renal impairment including patients requiring dialysis (CrCl < 30 ml/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 TEMADEX in these patients.

Elderly patients:

After administration of TEMADEX 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 to 64 years) was 2,2 minutes, in elderly adults (65 to 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 TEMADEX 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 TEMADEX is mainly excreted renally no dose adjustments are required.

Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of TEMADEX in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy (see **section 4.4**).

Children and adolescents:

For reversal of rocuronium induced blockade at reappearance of T_2 in children and adolescents (7 to 17 years) 2 mg/kg TEMADEX is recommended.

Immediate reversal in children and adolescents has not been investigated and is therefore not recommended.

TEMADEX 100 mg/ml may be diluted to 10 mg/ml to increase the accuracy of dosing in the paediatric population, 7 years and older.

Paediatric population:

The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T2). There is insufficient information on the use of TEMADEX for children < 7 years of age. There is no information on TEMADEX use for neonates. Therefore, TEMADEX is not recommended for use in these populations.

Method of administration:

TEMADEX should be administered under the supervision of an anaesthetist.

TEMADEX should be administered intravenously as a single bolus injection. The bolus injection may be given rapidly, within 10 seconds, directly into a vein or into an existing IV line.

4.3 Contraindications:

- Hypersensitivity to sugammadex sodium or to any of the excipients listed in **section 6.1**.

4.4 Special warnings and precautions for use:

TEMADEX is not to be used to reverse depolarising neuromuscular blocking agents. Waiting times for re-administration with neuromuscular blocking agents (NMBA) after reversal with TEMADEX.

Re-administration of rocuronium or vecuronium after a recommended dose reversal (up to 4 mg/kg TEMADEX):

Minimum waiting time	**NMBA (e.g Esmeron) and dose to be administered**
5 minutes	1,2 mg/kg rocuronium
4 hours	0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium

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

Based on PK modelling the recommended waiting time in patients with mild or moderate renal impairment for re-use of 0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium after routine reversal with TEMADEX should

be 24 hours. If a shorter waiting time is required, the rocuronium dose for a new neuromuscular blockade should be 1,2 mg/kg.

Re-administration of rocuronium or vecuronium after immediate reversal (16 mg/kg TEMADEX): A waiting time of 24 hours is recommended.

If neuromuscular blockade is required before the recommended waiting time has passed, a **non-steroidal neuromuscular blocking agent** should be used. The onset of a depolarising neuromuscular blocking agent might be slower than expected, because a substantial fraction of post-junctional nicotinic receptors may still be occupied by the neuromuscular blocking agent.

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.

Medicine hypersensitivity:

Doctors should be prepared for the possibility of medicine hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions (see **section 4.8**).

Renal impairment:

TEMADEX is not recommended for use in patients with severe renal impairment, creatinine clearance < 30 ml/min, including requiring dialysis (see **section 5.1**).

Because of the estimated prolonged half-life of TEMADEX in severe renally impaired patients, a full neuromuscular blockade may not be achieved after re-use of 0,6 mg/kg rocuronium or 0,1 mg/kg vecuronium within 24 hours after TEMADEX reversal.

Marked bradycardia:

Marked bradycardia has been observed within minutes after the administration of TEMADEX for reversal of neuromuscular blockade. Cases of bradycardia with cardiac arrest have been reported (see **section 4.8**). Patients should be closely monitored for haemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anticholinergic medicines such as atropine should be administered if clinically significant bradycardia is observed.

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 medicines used in the peri- and post-operative period could depress respiratory function and therefore ventilatory support might still be required.

Should neuromuscular blockade re-occur 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 *in-vitro* experiments additional aPTT and PT prolongation was noted for TEMADEX in combination 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 TEMADEX 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 16 mg/kg TEMADEX.

If there is a medical need to give TEMADEX 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 TEMADEX is administered to these patients monitoring of haemostasis and coagulation parameters is recommended.

In a study in volunteers, doses of 4 mg/kg and 16 mg/kg of TEMADEX resulted in maximum mean prolongations of the activated partial thromboplastin time (aPTT) by 17 and 22 % respectively and of prothrombin time international normalized ratio [PT (INR)] by 11 and 22 % respectively. These limited mean aPTT and PT (INR) prolongations were of a short duration ($\leq$ 30 minutes).

Based on the clinical database (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 TEMADEX 4 mg/kg alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications.

Since there is no information on the use of TEMADEX in patients with known coagulopathies, coagulation parameters should be carefully monitored according to routine clinical practice.

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.

Hepatic impairment:

TEMADEX is not metabolised nor excreted by the liver; therefore dedicated studies in patients with hepatic impairment have not been conducted. Patients with hepatic impairment should be treated with great caution. Hepatic impairment may be accompanied by coagulopathy (see information on the *Effect on haemostasis* above).

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 sucking 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.

Use in Intensive Care Unit (ICU):

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

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

TEMADEX should not be used to reverse block induced by non-steroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds.

TEMADEX should not be used for reversal of neuromuscular blockage 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 blockage, but it is advised not to use TEMADEX in this situation.

Sodium:

TEMADEX contains up to 9,7 mg sodium per mL, equivalent to 0,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction:

The information in this section is based on binding affinity between TEMADEX and other medicines, nonclinical 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 TEMADEX.

Based on these data, no clinically significant pharmacodynamic interaction with other medicines 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 TEMADEX (displacement interactions):

Due to the administration of certain medicines after TEMADEX, 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 medicine 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 medicine occurring within a period of 7,5 hours after TEMADEX 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. Medical practitioners 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 TEMADEX see **section 4.2**.

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

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

Hormonal contraceptives:

The interaction between 4 mg/kg TEMADEX 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 TEMADEX is considered

to be equivalent to one missed daily dose of **oral** contraceptive steroids (either combined or progestogen only). If TEMADEX 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 medicines 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 medicines which potentiate neuromuscular blockade. In case recurrence of neuromuscular blockade is observed, the patient may require mechanical ventilation and re-administration of TEMADEX (see **section 4.2**).

Interference with laboratory tests:

In general TEMADEX 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 microgram/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 TEMADEX 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:

The safety in pregnant women has not been established.

Breastfeeding:

Excretion of sugammadex in human milk has not been studied, but can be expected based on the pre-clinical data.

Fertility:

The effects with TEMADEX 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:

TEMADEX has no influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile:

TEMADEX is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess.

The most frequently reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication.

b) Tabulated summary of adverse reactions:

The safety of TEMADEX has been evaluated based on an integrated safety database of approximately 1700 patients and 120 volunteers.

System organ class	**Frequencies**	**Adverse reactions**
Immune system disorders	Less frequent	Medicine hypersensitivity reactions (see **section 4.4**)
Nervous system disorders	Frequent	Dysgeusia
Respiratory, thoracic and mediastinal disorders	Frequent	Cough
Injury, poisoning and procedural complications	Frequent	Airway complication of anaesthesia Procedural hypotension Procedural complication Prolonged neuromuscular blockade
	Less frequent	Anaesthetic complication (see **section 4.4**)

c) Description of selected adverse reactions:

Medicine 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 less frequently 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, was judged to be related to treatment in about 1 % of the patients and in none of the placebo group. Most occurrences of anaesthetic complications were mild to moderate. 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**).

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 medical practitioner 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.

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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reactions Reporting Form**', found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

Overdose may precipitate or exacerbate side effects.

TEMADEX 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:

A.34 Other

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 0.5 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.

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 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:

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 84 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

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.

Predicted pharmacokinetic parameters of sugammadex by age group and renal function based on compartmental modelling are presented below:

Selected patient characteristics			**Mean predicted PK parameters (CV %)**		
Demographics	Renal function Creatinine clearance (ml/min)		Clearance ml/min	Volume of distribution at steady state (L)	Elimination half-life (hr)
Adult	Normal	100	84 (22%)	11,9	2 19%)
40 yrs	Impaired	50	48 (22%)	13,1	3,6 (20%)
75 kg		30	29 (23%)	13,7	6,1 (21%)
		10	9 (19%)	14,2	20,3 (20%)
Elderly	Normal	80	72 (26%)	12,4	2,4 (23%)
75 yrs	Impaired	50	49(22%)	13,1	3,5 (19%)
75 kg		30	29 (22%)	13,7	6,1 (20%)
		10	8 (19%)	14,2	21,0 (23%)
Adolescent	Normal	95	76 (20%)	9,3	1,7 (17 %)
15 yrs	Impaired	48	45 (24%)	10,1	3,0 (21 %)
56 kg		29	26 (22%)	10,5	5,2 (19%)
		10	7 (18%)	10,9	17,8 (l8%)
Child	Normal	51	40 (21 %)	4,3	1,5 (16%)
7 yrs	Impaired	26	20 (20%)	4,5	2,9 (19 %)
23 kg		15	11 (27%)	4,6	5,2 (24 %)
		5	3 (22%)	4,7	19,4 (23 %)

CV=coefficient of variation

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 2 mg/kg and 4 mg/kg was dosed according to actual body weight or ideal body weight. 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Hydrochloric acid (to adjust pH)

Sodium hydroxide (to adjust pH)

Water for injections

6.2 Incompatibilities:

TEMADEX must not be mixed with other medicines except those mentioned in **section 6.6**.

Physical incompatibility has been reported with verapamil, ondansetron and ranitidine.

6.3 Shelf life:

18 months

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 medicine, see **section 6.3**.

6.5 Nature and contents of container:

The solution is supplied as a single-dose, in a colourless type I glass vial, closed with type I rubber stopper and sealed by an aluminium cap with coloured polypropylene disk.

Pack sizes: 10 vials of 2 ml or 10 vials of 5 ml. Packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

TEMADEX can be injected into the intravenous line of a running infusion with the following intravenous solutions: sodium chloride 9 mg/ml (0,9 %), glucose 50 mg/ml (5 %), sodium chloride 4.5 mg/ml (0,45 %) and glucose 25 mg/ml (2,5 %), Ringers lactate solution, Ringers solution, glucose 50 mg/ml (5 %) in sodium chloride 9 mg/ml (0,9 %).

The infusion line should be adequately flushed (e.g., with 0,9% sodium chloride) between administration of TEMADEX and other medicines.

Use in the paediatric population:

For paediatric patients TEMADEX can be diluted using sodium chloride 9 mg/ml (0,9 %) to a concentration of 10 mg/ml (see **section 6.3**).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBER(S):

TEMADEX 200: 55/34/0899

TEMADEX 500: 55/34/0900

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

09 May 2023

10. DATE OF REVISION OF THE TEXT: