1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

DIRADEX, 200 mg/2 mL

Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 mg sugammadex equivalent to 108,8 mg sugammadex sodium.

Each 2 mL contains 200 mg sugammadex equivalent to 217,6 mg sugammadex sodium.

Excipient(s) with known effect

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

Sugar content: Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.

Clear and colourless to slightly yellow solution with a pH of between 7 and 8 and osmolality is between 300 and 500 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

DIRADEX is indicated for:

- the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium.

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

Paediatrics

DIRADEX is only recommended for the routine reversal of rocuronium induced blockade in children above 7 years of age.

4.2 Posology and method of administration

Posology

DIRADEX should be administered under the supervision of an anaesthetist.

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 DIRADEX, patients should be monitored for signs of recurrence of neuromuscular blockade.

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

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

Adults

Routine Reversal of Neuromuscular Blockade

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

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

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

Additional information on special population

Elderly

After administration of DIRADEX 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).

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 DIRADEX 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 DIRADEX in these patients.

Hepatic impairment

For mild to moderate hepatic impairment: As DIRADEX 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 DIRADEX in patients with severe hepatic Impairment or when hepatic impairment is accompanied by coagulopathy (see section 4.4).

Other relevant special populations

Obese Patients

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

Paediatric population

The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T_2). There is insufficient information on the use of DIRADEX for children < 7 years of age. There is no information on DIRADEX use for neonates. Therefore DIRADEX is not recommended for use in these populations.

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 DIRADEX is recommended.

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

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

Method of administration

DIRADEX 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.

DIRADEX has only been administered as a single bolus injection in clinical trials.

For compatibility of DIRADEX with infusion solutions (see section 6.4).

4.3 Contraindications

DIRADEX is contraindicated in patients with known hypersensitivity to sugammadex sodium or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

DIRADEX is not to be used to reverse depolarising neuromuscular blocking agents.

Waiting times for re-administration with neuromuscular blocking agents (NMBA) after reversal with DIRADEX.

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

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

The onset of neuromuscular blockade may be prolonged up to approximately 4 minutes, and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes after re-administration of rocuronium 1,2 mg/kg within 30 minutes after sugammadex administration.

Based on PK modelling the recommended waiting time in patients with mild or moderate renal impairment for re-use of 0,6 mg/kg rocuronium or
0,1 mg/kg vecuronium after routine reversal with sugammadex should be 24 hours. If a shorter waiting time is required, the rocuronium dose

for a new neuromuscular blockade should be 1,2 mg/kg.

Re-administration of rocuronium or vecuronium after Immediate reversal (16 mg/kg sugammadex): 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.

Medicine Hypersensitivity

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

Renal Impairment

DIRADEX is not recommended for use in patients with severe renal impairment, creatinine clearance < 30 mL/min, including requiring dialysis (see section 5.21).

Because of the estimated prolonged half-life of sugammadex 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 sugammadex reversal.

Marked Bradycardia

Marked bradycardia has been observed within minutes after the administration of DIRADEX 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 agents 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.

Effect on Haemostasis

In a study in volunteers, doses of 4 mg/kg and 16 mg/kg of sugammadex sodium as in DIRADEX 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 short duration (≤ 30 minutes). Based on the clinical database there was no clinically relevant effect of sugammadex as in DIRADEX 4mg/kg alone or in combination with anticoagulants on the incidence of peri- or post-operative bleeding complications.

In *in-vitro* experiments additional aPTT and PT prolongation was noted for sugammadex as in DIRADEX 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 DIRADEX 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 DIRADEX

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

DIRADEX 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.

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)

DIRADEX 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

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

Sodium

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

Recurrence of Neuromuscular Blockade

Inclinical 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 increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended (see section 4.2 and section 4.8)

4.5 Interactions with other medicines and other forms of interaction

The information reported in this section is based on binding affinity between DIRADEX and other medicines, non-clinical experiments, clinical studies and simulations using a model taking into account the pharmacodynamic effect of neuromuscular blocking agents and sugammadex.

Based on these data, no clinically significant pharmacodynamic interaction with other medicines are expected, with the exception of toremifene, fusidic acid and hormonal contraceptives. For these medicines, a clinically relevant interaction could not be excluded.

Interactions potentially affecting the efficacy of sugammadex (displacement interactions)

No clinically relevant interactions were reported during the clinical development. Due to the administration of certain medicines after sugammadex, theoretically rocuronium or vecuronium could be displaced from DIRADEX. 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 DIRADEX administration.

DIRADEX should be used cautiously when co-administered with:

Toremifene

For toremifene, which has a relatively high binding affinity constant for sugammadex and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with DIRADEX could occur.

The recovery of the train of four ratio, T_4/T_1 to 0,9 could therefore be delayed in patients who have received toremifene on the same day of surgery.

Intravenous Administration of Fusidic Acid

The use of fusidic acid in the pre-operative phase may cause 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 to 3 days.

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

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

Hormonal Contraceptives

In a simulation performed with a PK-PD model, it was found that the interaction between 4 mg/kg sugammadex as in DIRADEX and a progestogen could 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 DIRADEX is considered to be equivalent to one missed daily dose of **oral** contraceptive steroids (either combined or progestogen only). Please refer to the missed dose advice in the package insert of the oral contraceptive, for any action required if an oral contraceptive is taken on the same day that DIRADEX is administered.

In the case of non-oral hormonal contraceptives, the patient must use an additional non-hormonal contraceptive method for the next 7 days.

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. In case recurrence of neuromuscular blockade is observed, the patient may require mechanical ventilation and re-administration of DIRADEX (see section 4.2).

Interference with Laboratory Tests

DIRADEX has been shown to interfere with the serum progesterone assay.

This interference was observed in plasma samples spiked with a concentration of DIRADEX in the same range as obtained for C_{max} after a dose of 16 mg/kg (see section 4.4).

Paediatric population

No formal interaction studies have been performed.

The above-mentioned interactions for adults and the warnings should also be taken into account for the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnant women has not been established.

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 DIRADEX to pregnant women.

Breastfeeding

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

Animal studies have shown excretion of sugammadex in breast milk.

Caution should be exercised when administering DIRADEX to breastfeeding women.

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

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

Patients should not drive, use machinery, or perform tasks that require concentration until they are certain that DIRADEX does not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

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

The most frequent reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications, procedural hypotension and procedural complication (Frequent (≥ 1/100 to < 1/10)).

b. Tabulated summary of adverse reactions

The safety of DIRADEX has been evaluated based on an integrated safety database and the following adverse reactions were reported:

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, anaesthetic complication (see section 4.4), procedural hypotension, procedural complication, prolonged neuromuscular blockade (common with sub-optimal doses).

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 frequent 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 DIRADEX.

Symptoms associated with these reactions can include: Flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of tongue, swelling of the 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 complications

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 sucking 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.

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 Healthy Volunteers

Hypersensitivity reactions, including anaphylaxis, have been observed with sugammadex as in DIRADEX. ln a study in healthy conscious volunteers (placebo, 4 mg/kg, and 16 mg/kg, hypersensitivity reactions were reported frequently with sugammadex as in DIRADEX 16 mg/kg and less frequent with DIRADEX 4 mg/kg or placebo. In this study, dose dependent trends were also observed for dysgeusia, nausea and flushing.

d. Paediatric population

A limited database suggests that the safety profile of DIRADEX (up to 4 mg/kg) in paediatric patients above 7 years old was similar to that in adults.

e. Other special population(s)

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.

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 I to III studies (see Tabulated summary of adverse reactions).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety

APP (Medsafety SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

DIRADEX can be removed using haemodialysis with a high-flux filter, but not with a low-flux filter. Based upon clinical studies, DIRADEX concentrations in plasma are reduced with a high-flux filter by about 70 % after a 3 to 6 hour dialysis session.

5. PHARMACOLOGICAL PROPERTIES

Sugammadex

5.1 Pharmacodynamic properties

A.34 Other

Pharmacotherapeutic group: All other therapeutic products, antidotes

ATC code: V03AB35

Mechanism of action

Sugammadex sodium injection is a modified gamma cyclodextrin. It is a selective relaxant binding agent (SRBA) which forms a complex with the neuromuscular blocking agents rocuronium and vecuronium in plasma, therefore reducing 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 and 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 sodium is approximately 11 to 14 litres in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Neither sugammadex nor rocuronium bind to plasma proteins or erythrocytes. Sugammadex sodium exhibits linear kinetics in the dose range of 1 to 16 mg/kg when administered as an IV bolus dose.

Biotransformation

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 anaesthetised patients with normal renal function the elimination half-life of sugammadex sodium 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. Ninety six percent
(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 < 0,02 % of the dose. Administration of sugammadex sodium 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 approximately 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 t½ 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.

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

Selected patient characteristics			Predicted PK parameters		
Demographics	Renal function (creatine clearance in ml/min)		Clearance in ml/min (CV)	Volume of distribution at steady state in litres	Elimination half-life in hours (CV)
Adult 40 years 75 kg	Normal	100	84 (22 %)	11,9	2,0 (19 %)
	Impaired	50 30 10	48 (22 %) 29 (23 %) 9 (19 %)	13,1 13,7 14,2	3,6 (20 %) 6,1 (21 %) 20,3 (20 %)
Elderly	Normal	80	72 (26 %)	12,4	2,4 (23 %)

75 years 75 kg	Impaired	50 30 10	49 (22 %) 29 (22 %) 8 (19 %)	13,1 13,7 14,2	3,5 (19 %) 6,1 (20 %) 21,0 (23 %)
Adolescent 15 years 56 kg	Normal	95	76 (20 %)	9,3	1,7 (17 %)
	Impaired	48 29 10	45 (24 %) 26 (22 %) 7 (18 %)	10,1 10,5 10,9	3,0 (21 %) 5,2 (19 %) 17,8 (18 %)
Child 7 years 23 kg	Normal	51	40 (21 %)	4,3	1,5 (16 %)
	Impaired	26 15 5	20 (20 %) 11 (27 %) 3 (22 %)	4,5 4,6 4,7	2,9 (19 %) 5,2 (24 %) 19,4 (23 %)

Mean and coefficient of variation (CV in %) are presented. For Volume of distribution, no CV could be estimated from the model.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (pH adjuster), diluted hydrochloric acid (pH adjuster),

water for injection and nitrogen.

6.2 Incompatibilities

This medicine 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

24 months

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

6.4 Special precautions for storage

DIRADEX 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 %). Ringer's lactate solution, Ringer's solution, glucose 50 mg/mL (5 %) in sodium chloride 9 mg/mL (0,9 %).

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

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

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

6.5 Nature and contents of container

DIRADEX is packaged in a 2 mL clear, borosilicate, type I glass vial with a chlorobutyl rubber stopper and a pale brown aluminium plastic cap.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Encha Health (Pty) Ltd

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Maxwell Office Park

Waterfall City

1662

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8. APPLICATION NUMBER(S)

Unregistered medicine: 561211

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10. DATE OF REVISION OF THE TEXT

Not applicable