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**SCHEDULING STATUS**

**S4**

**1. NAME OF THE MEDICINE**

**Alepet 4** (solution for injection)

**Alepet 8** (solution for injection)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

**Alepet 4 :** 2 mg/ml ondansetron (as ondansetron hydrochloride dihydrate)

**Alepet 8 :** 2 mg/ml ondansetron (as ondansetron hydrochloride dihydrate)

Excipient with known effect: 1 ml solution for injection or infusion contains 3,6 mg of sodium as sodium citrate, sodium chloride and sodium hydroxide.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Injection

**Alepet 4:** A clear colourless solution free from visible particles.

**Alepet 8:** A clear colourless solution free from visible particles.

**4. CLINICAL PARTICLUARS**

**4.1 THERAPEUTIC INDICATIONS:**

Alepet is indicated for the management of nausea and vomiting induced by chemotherapy and radiotherapy.

Alepet is also indicated for the prevention and treatment of post operative nausea and vomiting.

Routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and vomiting will occur.

**4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

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***Chemotherapy and radiotherapy induced nausea and vomiting:***

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

***Adults:***

***Emetogenic Chemotherapy and Radiotherapy:***

For most patients receiving emetogenic chemotherapy or radiotherapy, Alepet 8 mg should be administered as a slow IV (not less than 2-3 minutes) or IM injection in not less than 30 seconds, immediately before treatment.

***Highly Emetogenic Chemotherapy****:*

A single dose of Alepet 8 mg by slow IV (not less than 2-3 minutes) or IM injection in not less than 30 seconds, immediately before chemotherapy has been shown to be effective in many patients. Higher doses may be required in some patients, particularly those on high dose cisplatin, and the doses should be adjusted according to the severity of the emetogenic challenge. In these patients the following dose schedules have been shown to be effective:

A dose of 8 mg by slow IV or IM injection immediately before chemotherapy, followed by two further IV or IM doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

OR ALTERNATIVELY

A maximum single IV dose of ~~32~~ 16 mg diluted in 50-100 ml of saline 0,9 % NaCl) or other compatible infusion fluid infused over not less than 15 minutes immediately before chemotherapy. A single dose greater than 16 mg should not be given due to dose-dependent increased risk of QT prolongation (see section 4.4).

The efficacy of Alepet in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone phosphate 20 mg administered 30-45 minutes prior to the first Alepet dose prior to chemotherapy.

***Children:***

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Experience is currently limited but Alepet was effective and well tolerated in children over the ages of 4 years, when given intravenously at a dose of 5 mg/m$^2$ over 15 minutes, immediately before chemotherapy.

***Elderly patients:***

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults.
Specific dosing information for intravenous dosing is provided for patients over 65 years of age and over 75 years of age.

*Elderly patients aged 75 years or older:*

- A single dose of intravenous Alepet given for the prevention of chemotherapy-induced nausea and vomiting (CINV) must not exceed 8 mg (infused over at least 15 minutes).

*Adult patients aged less than 75 years:*

- A single dose of intravenous Alepet given for the prevention of CINV in adults (aged less than 75 years) must not exceed 16 mg (infused over at least 5 minutes).

Elderly patients aged 65 years or older:

- All intravenous doses should be diluted in 50-100 ml saline or other compatible fluid and infused over at least 15 minutes.
- Repeat intravenous doses of Alepet should be given no less than 4 hours apart.

***Patients with Renal Impairment:***

No alteration of daily dosage or frequency of dosing, or route of administration are required.

***Patients with Hepatic Impairment:***

Clearance of Alepet is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded and therefore parenteral or oral administration is recommended.

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***Prevention and treatment of post-operative nausea and vomiting:***

***Adults:***

Immediately before induction of anaesthesia, or post-operatively if the patient experiences nausea and/or vomiting occurring shortly after surgery, administer 4 mg undiluted intramuscularly or intravenously. If given intravenously it must be administered over not less than 2-5 minutes or longer.

*Children:*

For prevention of post-operative nausea and vomiting in paediatric patients two years and older having surgery performed under general anaesthesia, Alepet may be administered by slow intravenous injection over 2 to 5 minutes or longer at a dose of 0,1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia. For the treatment of established post-operative nausea and vomiting in paediatric patients two years and older, Alepet may be administered by slow intravenous injection at a dose of 0,1 mg/kg up to maximum of 4 mg over not less than 2-5 minutes or preferably longer. Repeat dosing for paediatric patients who continue to experience nausea and/or vomiting has not been studied, and should thus not be given.

*Elderly:*

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults.

Specific dosing information for intravenous dosing is provided for patients over 65 years of age and over 75 years of age.

A slight age-related decrease in clearance, and an increase in the half-life of ondansetron is predicted, presenting as slight, clinically insignificant age-related increases in both oral bioavailability (65 %) and a prolonged elimination half-life (5 hours) of ondansetron.

***Patients with renal/hepatic impairment:***

*Patients with renal impairment:*

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No alteration of daily dosage or frequency of dosing, or route of administration are required for mild or moderate renal impairment. There is limited information available for daily dosage or frequency of dosing, or route of administration for severe renal impairment.

*Patients with hepatic impairment:*

Clearance of Alepet is significantly reduced and serum half-life significantly prolonged in severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

**4.3 CONTRA-INDICATIONS**

Alepet is contra-indicated in:

- patients known to have hypersensitivity to ondansetron or to any components of the preparation (see section 6.1)
- Concomitant use with apomorphine (see section 4.5)
- Alepet is contraindicated during the first 12 weeks of pregnancy irrespective of the indication, due to an increased risk of developing oral cleft palate and/or lip to the foetus (see section 4.4).
- post-operative nausea and vomiting in pregnancy (see section 4.6)
- Congenital long QT syndrome.

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Cross-hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

Respiratory events should be treated symptomatically, and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Alepet prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron, as in Alepet. Avoid Alepet in patients with congenital long QT syndrome (see section 4.3). Alepet should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradydysrhythmias or patients taking other medicines that lead to QT prolongation or

electrolyte abnormalities.

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration,
symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischemia.

Hypokalaemia and hypomagnesaemia should be corrected prior to Alepet administration.

Post-marketing reports describe patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic medicines (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with Alepet and other serotonergic medicines is clinically warranted, appropriate close observation of the patient is advised.

As Alepet is known to increase large bowel transit time, patients with signs of intestinal obstructions should be closely monitored following administration.

In patients with adenotonsillar surgery prevention of nausea and vomiting with Alepet may mask occult bleeding. Therefore, such patients should be carefully monitored after Alepet.

The use of Alepet during the first 12 weeks of pregnancy increases the risk of developing oral cleft palate and or lip to the foetus (se section 4.3).

*Patients with hepatic impairment:*
Clearance of Alepet is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

*Paediatric population*

The daily dose for children should not exceed 4 mg.

Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic medicines should be closely monitored for impaired hepatic function.

Alepet contains sodium, this should be taken into consideration by patients on a sodium restricted diet.

**4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicines commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, morphine, lidocaine, thiopental, or propofol.

***Apomorphine:***

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered concomitantly with apomorphine hydrochloride concomitant use with apomorphine is contraindicated (see section 4.3).

Ondansetron is metabolised by multiple hepatic cytochrome P450 enzymes CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated for by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirements.

Caution must be exercised when ondansetron is co-administered with other medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Co-administration of ondansetron with QT prolonging medicines may result in additional QT-prolongation. Concomitant use of ondansetron with cardiotoxic medicines (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antidysrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of dysrhythmias (see section 4.4).

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***Serotonergic Medicines (e.g. SSRIs and SNRIs):***

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

Blood concentrations of Alepet were decreased with concomitant administration with phenytoin, carbamazepine, and rifampicin (potent inducers of CYP3A4), causing reduced anti-emetic efficacy.

Alepet may reduce the analgesic effect of tramadol.

**4.6 FERTILITY, PREGNANCY AND LACTATION**

***Women of child bearing potential***

Women of childbearing potential being treated with Alepet should not become pregnant as Alepet is contraindicated in the first 12 weeks of pregnancy, irrespective of the cause of the nausea and vomiting (see section 4.3).

***Pregnancy****:*

Alepet is contraindicated for post-operative nausea and vomiting during pregnancy, as well as during the first 12 weeks of pregnancy irrespective of the indication due
to the risk (see section 4.3).
During the first 12 weeks of pregnancy can be associated with an increased risk of developing oral cleft palate and/or lip to the foetus.

***Breastfeeding:***

Ondansetron passes into the milk of lactating animals. Mothers receiving Alepet should not breast feed their babies.

***Fertility:***

There is no information on the effects of ondansetron on human fertility.

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## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Alepet causes nervous system and eye disorders which may adversely affect the ability of patients to drive or operate machines.

Patients on with Alepet should therefore not drive or use machines until the effects of Alepet treatment are known (see section 4.8).

## 4.8 UNDESIRABLE EFFECTS

*Tabulated summary of adverse reactions*

| System organ class | Frequency | Adverse reaction |
|---|---|---|
| **Immune system disorders** | Less frequent | Immediate hypersensitivity reactions, sometimes severe (e.g. anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria) |
| **Nervous system disorders** | Frequent | Headache |
| | Less frequent | Seizures, dizziness during or shortly after rapid intravenous administration. Movement disorders including extrapyramidal reactions such as dystonic reactions, oculogyric crises and dyskinesia have been observed. |
| **Eye disorders** | Less frequent | Transient visual disturbances (e.g. blurred vision) and blindness during or shortly after rapid intravenous administration.<br>The majority of the blindness cases reported resolved within 20 minutes. Most patients had |

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| | | |
|---|---|---|
| | | received chemotherapeutic medicines which included cisplatin. Some cases of transient blindness were reported as cortical in origin. |
| **Cardiac disorders** | Less frequent | Dysrhythmias, bradycardia, chest pain with or without ST segment depression.<br>QTc prolongation (including Torsades de Pointes |
| | Frequency unknown | Myocardial ischaemia (see section 4.4) |
| **Vascular disorders** | Frequent | Sensations of flushing or warmth |
| | Less frequent | Hypotension |
| **Respiratory, thoracic and mediastinal disorders** | Less frequent | Hiccups.<br>Respiratory events: should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions. |
| **Gastro-intestinal disorders** | Frequent | Increase in large bowl transit time and constipation. |
| **Hepato-biliary disorders** | Less frequent | Asymptomatic increases of liver enzymes. These events were commonly observed in patients receiving cancer chemotherapy with cisplatin. |
| **General disorders and administration site conditions** | Frequent | Pain, redness and burning at site of injection. |

Reporting of suspected adverse reactions

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Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

**4.9 OVERDOSE**

In the majority of cases symptoms were similar to or an extension of those already reported in patients receiving the recommended doses (see section 4.8).

Manifestations include severe constipation, visual disturbances, hypotension and a vasovagal episode with transient second degree AV block.

Ondansetron prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, as there is no specific antidote for ondansetron. Further management should be as clinically indicated or as recommended by the national

poisons centre, where available.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 PHARMACODYNAMIC PROPERTIES**

Category and class: A 5.10 Medicines affecting autonomic functions. Serotonin antagonists.

Pharmacotherapeutic group: Serotonin (5HT3) antagonist, ATC code: A04AA01

***Mechanism of action***

Ondansetron is a potent selective 5-$HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known.

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Chemotherapeutic medicines and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-$HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is due to antagonism of 5-$HT_3$ receptors on neurons located both in the peripheral and central nervous system. In psychomotor testing ondansetron does not impair performance nor cause sedation.

The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxically-induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established.

**5.2 PHARMACOKINETIC PROPERTIES**

Following oral administration of ondansetron, absorption is rapid with maximum plasma concentrations of about 30 ng/ml being attained approximately 1,6 hours after an 8 mg dose. The absolute oral bioavailability of ondansetron is approximately 60 %. The disposition of ondansetron following both oral and intravenous dosing is similar with a terminal elimination half-life of about 3 hours and a steady-state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

Plasma protein binding is 70-76 %. Ondansetron is cleared from the systemic circulation predominantly by metabolism with less than 5 % of a dose excreted unchanged in the urine.

The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Studies in healthy elderly volunteers have shown a slightly increased oral bioavailability (65 %) and prolonged elimination half-life (5 hrs) for ondansetron.

***Special patient populations***

*Elderly*

Studies showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for intravenous dosing patients over 65 years of age and over 75 years of age.

*Renal impairment*

In patients with renal impairment (creatinine clearance 15 – 60 ml/min), systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant increase in elimination half-life (5,4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged.

*Hepatic impairment*

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 hrs) and an oral bioavailability approaching 100 %.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Sodium chloride

Sodium citrate

Citric acid monohydrate

Sodium hydroxide (for pH adjustment)

Hydrochloric acid concentrates (for pH adjustment)

### 6.2 INCOMPATIBILITIES

Alepet should not be administered in the same syringe or infusion as any other medication. Alepet should only be mixed with those infusion solutions that are recommended (see section 6.6).

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**6.3 SHELF-LIFE**

3 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store at or below 25 ˚C.

Keep the ampoules in the carton until required for use.

Protect from light.

Intravenous solutions should be prepared at the time of infusion. However, when diluted with the recommended IV solutions, Alepet been shown to be stable for seven days at room temperature (below 25 ˚C) or in a refrigerator (between 2-8 ˚C).

**6.5 NATURE AND CONTENTS OF CONTAINER**

**Alepet 4**: A 2 ml type I clear colourless glass ampoule with a red band and a red OPC dot, filled with 2 ml of solution, 5 ampoules per unit carton.

**Alepet 8**: A 5 ml type I clear colourless glass ampoule with a red band and a red OPC dot, filled with 4 ml of solution, 5 ampoules per unit carton.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

Alepet injection ampoules should not be autoclaved.

*Compatibility with intravenous fluids:*

Alepet injection should only be admixed with those infusion solutions which are recommended below. In keeping with good pharmaceutical practice, intravenous solutions should be prepared at the time of infusion.

However, Alepet injection has been shown to be stable for seven days at room temperature (below 25 ˚C) or in a refrigerator (between 2-8 ˚C) with the following infusion fluids:

Sodium Chloride Intravenous Infusion BP 0,9 % m/v.

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Glucose Intravenous Infusion BP 5 % m/v.

Ringers Intravenous Infusion.

Potassium Chloride 0,3 % m/v and Sodium Chloride 0,9 % m/v Intravenous Infusion BP.

Potassium Chloride 0,3 % m/v and Glucose 5 % m/v Intravenous Infusion BP.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type 1 glass bottles. Dilutions of ondansetron in sodium chloride 0,9 % m/v or in glucose 5 % m/v have been demonstrated to be stable in polypropylene syringes. It is considered that Alepet injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Note: Preparation must be under the appropriate aseptic conditions if extended storage periods are required.

*Compatibility with other medicines:*

NOTE: As a general principle it is not recommended to mix medicines for infusion. Alepet injection may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following medicines may be administered via the Y-site of the Alepet giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively).

*Cisplatin:*

Concentrations up to 0,48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

*Dexamethasone:*

Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 mg of Alepet diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and Alepet has been demonstrated supporting administration of these medicines through the same giving set, with resulting in-line concentrations in the ranges of 32 µg-2,5 mg/ml for dexamethasone sodium phosphate and 8 µg-1 mg/ml for Alepet.

*Carboplatin:*

Concentrations in the range 0,18 mg/ml to 9,9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

*Etoposide:*

Concentrations in the range 0,14 mg/ml to 0,25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

*Ceftazidime:*

Doses in the range 250 mg to 2000 mg reconstituted with Water for Injection BP, as recommended by the manufacturer (e.g. 2,5 ml for 250 mg and 10 ml for 2 g ceftazidime), and given as an intravenous bolus injection over approximately five minutes.

*Cyclophosphamide:*

Doses in the range 100 mg to 1 g, reconstituted with Water for Injection BP,
5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

*Doxorubicin:*

Doses in the range 10-100 mg reconstituted with Water for Injection BP, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Accord Healthcare (Pty) Ltd
Building 31, Ground Floor,
Woodlands Office Park,
20 Woodlands Drive, Woodmead,
Johannesburg, 2191
Tel: +27 11 234 5701/2

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Email: medinfo@accordhealth.co.za

**8. REGISTRATION NUMBERS**

**ALEPET 4** : 42/5.10/0891

**ALEPET 8** : 42/5.10/0892

**9. DATE OF FIRST AUTHORISATION**

30 September 2011

**10. DATE OF REVISION OF THE TEXT**

**28 November 2025**