**FINAL PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

EMETEND 150 mg (Powder for solution for infusion)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant.

After reconstitution and dilution 1 ml of solution contains 1 mg fosaprepitant (1 mg/ml) (see section 6.6).

Contains sugar (lactose)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off white lyophilised solid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

EMETEND 150 mg, in combination with other anti-emetic medicines, is indicated for the prevention of acute (0 to 24 hours) and delayed (> 24 to 120 hours) nausea and vomiting associated with initial and repeat courses of:

- Highly emetogenic cancer chemotherapy (see section 4.2)
- Moderately emetogenic cancer chemotherapy (see section 4.2)

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## 4.2 Posology and method of administration

Posology

EMETEND 150 mg for intravenous administration is a lyophilised prodrug of aprepitant.

The recommended dose is 150 mg administered as an infusion over 20-30 minutes on Day 1, initiated approximately 30 minutes prior to chemotherapy (see section 6.6).

Fosaprepitant should be administered in conjunction with a corticosteroid and a 5-$HT_3$ antagonist as specified in the tables below.

The professional information for the co-administered 5-$HT_3$ antagonist must be consulted prior to initiation of treatment with EMETEND 150 mg .

The following regimens recommended for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

**Table 1: Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy**

| | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| **EMETEND 150 mg** | 150 mg intravenously | none | none | none |
| **Dexamethasone**** | 12 mg orally | 8 mg orally | 8 mg orally twice daily | 8 mg orally twice daily |
| **5-$HT_3$** | See the professional information for the selected 5-$HT_3$ antagonist for the appropriate dosing information | none | none | none |

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**Table 2: Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy**

| | **Day 1** |
|---|---|
| **EMETEND 150 mg** | 150 mg intravenously |
| **Dexamethasone**** | 12 mg orally |
| **5-$HT_3$ antagonist** | See the professional information for the selected 5-$HT_3$ antagonist for appropriate dosing information. |

** Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1.

The dose of dexamethasone accounts for interactions.

Efficacy data in combination with other corticosteroids and 5-$HT_3$ antagonists are limited.

For additional information on the co-administration with corticosteroids, see section 4.5.

Refer to the professional information of co-administered 5-$HT_3$ antagonist medicinal products.

Special populations

*Elderly (≥ 65 years)*

No dose adjustment is necessary for the elderly (see section 5.2).

*Gender*

No dose adjustment is necessary based on gender (see section 5.2).

*Renal impairment*

No dose adjustment is necessary for patients with renal impairment or for patients with end stage renal disease undergoing haemodialysis (see section 5.2).

*Hepatic impairment*

No dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). There is no clinical data in patients with severe hepatic impairment (Child-Pugh > 9). Fosaprepitant should be used with caution in these patients (see sections 4.4 and 5.2).

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Paediatric population

The safety and efficacy of EMETEND 150 mg in children and adolescents below 18 years of age has not yet been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

EMETEND 150 mg should be administered intravenously and should not be given by the intramuscular or subcutaneous route. Intravenous administration occurs preferably through a running intravenous infusion over 20-30 minutes (see section 6.6).

Do not administer EMETEND 150 mg as a bolus injection or undiluted solution.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

### 4.3 Contraindications

- Hypersensitivity to aprepitant or any of the other excipients listed in section 6.1.
- Co-administration with pimozide or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these medicines potentially causing serious or life-threatening reactions. (see section 4.5).
- Pregnancy and lactation (see section 4.6)
- Safety and efficacy of EMETEND 150 mg in paediatric patients has not been established.

### 4.4 Special warnings and precautions for use

Patients with moderate to severe hepatic impairment

There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. EMETEND 150 mg should be used with caution in these patients (see section 5.2).

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CYP3A4 interactions

EMETEND 150 mg should be used with caution in patients receiving concomitant active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as ciclosporin, tacrolimus, sirolimus, everolimus, alfentanil, ergot alkaloid derivatives, fentanyl, and quinidine (see section 4.5). Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination might result in increased toxicity.

Concomitant administration of EMETEND 150 mg with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution.

The effect of oral aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of oral aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates.

Co-administration with warfarin (a CYP2C9 substrate)

In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely for 14 days following the use of fosaprepitant (see section 4.5).

Co-administration with hormonal contraceptives

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of fosaprepitant. Alternative non-hormonal back-up methods of contraception should be used during treatment with fosaprepitant and for one month following the use of fosaprepitant (see section 4.5).

Hypersensitivity reactions

Immediate hypersensitivity reactions including flushing, erythema, dyspnoea, and anaphylaxis/anaphylactic shock have occurred during or soon after infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. It is not recommended to reinitiate the infusion in patients who experience hypersensitivity reactions.

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Administration and infusion site reactions

Fosaprepitant should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see section 4.2). Fosaprepitant should not be administered intramuscularly or subcutaneously.

Infusion site reactions (ISRs) have been reported with the use of EMETEND 150 mg (see section 4.8). The majority of severe ISRs, including thrombophlebitis and vasculitis, were reported with concomitant vesicant (e.g. anthracycline-based) chemotherapy administration, particularly when associated with extravasation. Necrosis was also reported in some patients with concomitant vesicant chemotherapy. Mild injection site thrombosis has been observed at higher doses. If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

EMETEND 150 mg should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see section 4.2). EMETEND 150 mg should not be administered intramuscularly or subcutaneously. If signs or symptoms of local irritation occur, the injection or infusion should be terminated and restarted in another vein.

### 4.5 Interaction with other medicinal products and other forms of interaction

When administered intravenously fosaprepitant is rapidly converted to aprepitant.

Fosaprepitant 150 mg, given as a single dose, is a weak inhibitor of CYP3A4. Fosaprepitant does not seem to interact with the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin. It is anticipated that fosaprepitant would cause less or no greater induction of CYP2C9, CYP3A4 and glucuronidation than that caused by the administration of oral aprepitant. Data are lacking regarding effects on CYP2C8 and CYP2C19.

Interactions with other medicinal products following administration of intravenous fosaprepitant are likely to occur with active substances that interact with oral aprepitant. The following information was derived from studies conducted with oral aprepitant and studies

conducted with intravenous fosaprepitant co-administered with dexamethasone, midazolam, or diltiazem.

Effect of fosaprepitant on the pharmacokinetics of other active substances

*CYP3A4 inhibition*

As a weak inhibitor of CYP3A4, the fosaprepitant 150 mg single dose can cause a transient increase in plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of CYP3A4 substrates may increase up to 2-fold on Days 1 and 2 after co- administration with a single 150 mg fosaprepitant dose. Fosaprepitant must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by fosaprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life- threatening reactions. (See section 4.3). Caution is advised during concomitant administration of fosaprepitant and active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as ciclosporin, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see section 4.4).

*Corticosteroids*

Dexamethasone: The oral dexamethasone dose on Days 1 and 2 should be reduced by approximately 50 % when co-administered with fosaprepitant 150 mg on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without fosaprepitant 150 mg. Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, a CYP3A4 substrate, by 100 % on Day 1, 86 % on Day 2 and 18 % on Day 3 when dexamethasone was co-administered as a single 8 mg oral dose on Days 1, 2, and 3.

Methylprednisolone: Oral aprepitant, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1,3-fold on Day 1 and by 2,5-fold on Day 3, when methylprednisolone was co-administered

intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

*Paroxetine*

Co-administration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25 % and Cmax by approximately 20 % of both aprepitant and paroxetine.

*Chemotherapeutic medicinal products*

Interaction studies with fosaprepitant 150 mg and chemotherapeutic medicinal products have not been conducted; however, based on studies with oral aprepitant and docetaxel and vinorelbine, EMETEND 150 mg is not expected to have a clinically relevant interaction with intravenously administered docetaxel and vinorelbine. An interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g. etoposide, cyclophosphamide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products metabolized primarily or partly by CYP3A4 (see section 4.4). Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration.

*Immunosuppressants*

Following a single 150 mg fosaprepitant dose, a transient moderate increase for two days possibly followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g. ciclosporin, tacrolimus, everolimus and sirolimus) is expected. Given the short duration of increased exposure, dose reduction of the immunosuppressant based on Therapeutic Dose Monitoring is not recommended on the day of and the day after administration of fosaprepitant.

*Midazolam*

Fosaprepitant 150 mg administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by 77 % on Day 1 and had no effect on Day 4 when midazolam was

co-administered as a single oral dose of 2 mg on Days 1 and 4. Fosaprepitant 150 mg is a weak CYP3A4 inhibitor as a single dose on Day 1 with no evidence of inhibition or induction of CYP3A4 observed on Day 4.

The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicinal products with fosaprepitant.

*Diltiazem*

Interaction studies with fosaprepitant 150 mg and diltiazem have not been conducted; however, the following study with 100 mg of fosaprepitant should be considered when using EMETEND 150 mg with diltiazem. In patients with mild to moderate hypertension, infusion of 100 mg of fosaprepitant over 15 minutes with diltiazem 120 mg 3 times daily, resulted in a 1,4-fold increase in diltiazem AUC and a small but clinically meaningful decrease in blood pressure, but did not result in a clinically meaningful change in heart rate, or PR interval.

*Induction*

The fosaprepitant 150 mg single dose did not induce CYP3A4 on Days 1 and 4 in the midazolam interaction study. It is anticipated that fosaprepitant would cause less or no greater induction of CYP2C9, CYP3A4, and glucuronidation than that caused by the administration of the 3-day oral aprepitant regimen, for which a transient induction with its maximum effect 6-8 days after first aprepitant dose has been observed. The 3-day oral aprepitant regimen resulted in an about 30-35 % reduction in AUC of CYP2C9 substrates and up to a 64 % decrease in ethinyl estradiol trough concentrations. Data are lacking regarding effects on CYP2C8 and CYP2C19. Caution is advised when warfarin, acenocoumarol, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered with fosaprepitant.

*Warfarin*

In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with and for 14 days following the use of fosaprepitant for the

prevention of chemotherapy induced nausea and vomiting (see section 4.4).

*Hormonal contraceptives*

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of fosaprepitant. Alternative non-hormonal back-up methods of contraception should be used during treatment with fosaprepitant and for one month following the use of fosaprepitant.

*5-HT3 antagonists*

Interaction studies with fosaprepitant 150 mg and 5-$HT_3$ antagonists have not been conducted; however, in clinical interaction studies, the oral aprepitant regimen did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron). Therefore, there is no evidence of interaction with the use of fosiprepitant 150 mg and 5-$HT_3$ antagonists.

Effect of other medicinal products on the pharmacokinetics of aprepitant resulting from administration of fosaprepitant 150 mg

Concomitant administration of fosaprepitant with active substances that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone, and protease inhibitors) should be approached cautiously, as the combination is expected to result in several-fold increased plasma concentrations of aprepitant (see section 4.4). Ketoconazole increased the terminal half-life of oral aprepitant about 3-fold.

Concomitant administration of fosaprepitant with active substances that strongly induce CYP3A4 activity (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitone) should be avoided as the combination could result in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy. Concomitant administration of fosaprepitant with herbal preparations containing St. John's Wort (Hypericum perforatum) is not recommended. Rifampicin decreased the mean terminal half-life of oral aprepitant by 68 %.

Paediatric population

Interaction studies have only been performed in adults.

### 4.6 Fertility, pregnancy and lactation

Contraception in males and females

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of fosaprepitant. Alternative non-hormonal back-up methods of contraception should be used during treatment with fosaprepitant and for one month following the last dose of fosaprepitant (see sections 4.4 and 4.5).

Pregnancy

For fosaprepitant and aprepitant, no clinical data on exposed pregnancies are available. The potential for reproductive toxicities of fosaprepitant and aprepitant have not been fully characterised, since exposure levels above the therapeutic exposure in humans could not be attained in animal studies.

These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The potential effects on reproduction of alterations in neurokinin regulation are unknown.

EMETEND 150 mg should not be used during pregnancy.

Breast-feeding

Aprepitant is excreted in the milk of lactating rats after intravenous administration of fosaprepitant as well as after oral administration of aprepitant. It is not known whether aprepitant is excreted in human milk. Therefore, breast-feeding is not recommended during treatment with EMETEND 150 mg.

Fertility

The potential for effects of fosaprepitant and aprepitant on fertility has not been fully characterised because exposure levels above the therapeutic exposure in humans could not be attained in animal studies. These fertility studies did not indicate direct or indirect harmful

effects with respect to mating performance, fertility, embryonic/foetal development, or sperm count and motility.

### 4.7 Effects on ability to drive and use machines

EMETEND 150 mg may have an influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of EMETEND 150 mg (see section 4.8).

### 4.8 Undesirable effects

Summary of the safety profile

Since fosaprepitant is converted to aprepitant, those adverse reactions associated with aprepitant are expected to occur with fosaprepitant.

Oral aprepitant

The most common adverse reactions reported at a greater incidence in adults treated with the aprepitant regimen than with standard therapy in patients receiving Highly Emetogenic Chemotherapy (HEC) were: hiccups (4,6 % versus 2,9 %), alanine aminotransferase (ALT) increased (2,8 % versus 1,1 %), dyspepsia (2,6 % versus 2,0 %), constipation (2,4 % versus 2,0 %), headache (2,0 % versus 1,8%), and decreased appetite (2,0 % versus 0,5 %). The most common adverse reaction reported at a greater incidence in patients treated with the aprepitant regimen than with standard therapy in patients receiving Moderately Emetogenic Chemotherapy (MEC) was fatigue (1,4 % versus 0,9 %).

**Table 3: Tabulated list of adverse reactions - aprepitant**

| SYSTEM ORGAN CLASS | ADVERSE REACTION | FREQUENCY |
|---|---|---|
| **Infections and infestations** | candidiasis, staphylococcal infection | Less frequent |
| **Blood and lymphatic system disorders** | febrile neutropenia, anaemia | Less frequent |
| **Immune system disorders** | hypersensitivity reactions | not known |

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| | | |
|---|---|---|
| | including anaphylactic reactions | |
| **Metabolism and nutrition disorders** | decreased appetite | Frequent |
| | polydipsia | Less frequent |
| **Psychiatric disorders** | anxiety | Less frequent |
| | disorientation, euphoric mood | Less frequent |
| **Nervous system disorders** | headache | Frequent |
| | dizziness, somnolence | Less frequent |
| | cognitive disorder, lethargy, dysgeusia | Less frequent |
| **Eye disorders** | conjunctivits | Less frequent |
| **Ear and labyrinth disorders** | tinnitus | Less frequent |
| **Cardiac disorders** | palpitations | Less frequent |
| | bradycardia, cardiovascular disorder | Less frequent |
| **Vascular disorders** | hot flush / flushing | Less frequent |
| **Respiratory, thoracic and mediastinal disorders** | hiccups | Frequent |
| | oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation | Less frequent |
| **Gastrointestinal disorders** | constipation, dyspepsia | Frequent |
| | eructation, nausea*, vomiting*, gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence | Less frequent |
| | duodenal ulcer perforation, stomatitis, abdominal distension, faeces hard, neutropenic colitis | Less frequent |
| **Skin and subcutaneous tissue disorders** | rash, acne | Less frequent |
| | photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/toxic epidermal necrolysis | Less frequent |
| | pruritus, urticaria | not known |
| **Musculoskeletal and connective tissue disorders** | muscular weakness, muscle spasms | Less frequent |
| **Renal and urinary disorders** | dysuria | Less frequent |
| | pollakiuria | Less frequent |
| **General disorders and administration site conditions** | fatigue | Frequent |
| | asthaenia, malaise | Less frequent |
| | oedema, chest discomfort, gait disturbance | Less frequent |
| **Investigations** | ALT increased | Frequent |

| | | |
|---|---|---|
| | AST increased, blood alkaline phosphatase increased | Less frequent |
| | red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present | Less frequent |

* Nausea and vomiting were efficacy parameters in the first 5-days of post-chemotherapy treatment and were reported as adverse reactions only thereafter.

Description of selected adverse reactions

The adverse reactions profiles in the Multiple-Cycle extension of HEC and MEC studies in adults for up to 6 additional cycles of chemotherapy were generally similar to those observed in Cycle 1.

Additional adverse reactions were observed in adult patients treated with aprepitant for postoperative nausea and vomiting (PONV) and a greater incidence than with ondansetron: abdominal pain upper, bowel sounds abnormal, constipation*, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, sub-ileus*, visual acuity reduced, wheezing.

*Reported in patients taking a higher dose of aprepitant.

Fosaprepitant

The safety profile was generally similar to that seen in the aprepitant table above.

Tabulated list of adverse reactions - fosaprepitant

The following are adverse reactions reported in adult patients receiving fosaprepitant in clinical studies or postmarketing that have not been reported with aprepitant as described above:

**Table 4: Tabulated list of adverse reactions - fosaprepitant**

| SYSTEM ORGAN CLASS | ADVERSE REACTION | FREQUENCY |
|---|---|---|
| **Vascular disorders** | flushing, thrombophlebitis (predominantly, infusion-site thrombophlebitis | Less frequent |

| | | |
|---|---|---|
| **Skin and subcutaneous tissue disorders** | erythema | Less frequent |
| **General disorders and administration site conditions** | infusion site erythema, infusion site pain, infusion site pruritus | Less frequent |
| | infusion site induration | Less frequent |
| | immediate hypersensitivity reactions including flushing, erythema, dyspnoea, anaphylactic reactions/anaphylactic shock | not known |
| **Investigations** | blood pressure increased | Less frequent |

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 professionals 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

In the event of overdose, fosaprepitant should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, emesis induced by a medicinal product may not be effective.

Aprepitant cannot be removed by haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological classification: A 5.7.2 Anti-emetics and antivertigo preparations

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Fosaprepitant is the prodrug of aprepitant and when administered intravenously is converted rapidly to aprepitant (see section 5.2). The contribution of fosaprepitant to the overall antiemetic effect has not fully been characterised, but a transient contribution during the initial phase cannot be ruled out. Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 ($NK_1$) receptors. The pharmacological effect of fosaprepitant is attributed to aprepitant.

## 5.2 Pharmacokinetic properties

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant. Plasma concentrations of fosaprepitant are below quantifiable levels within 30 minutes of the completion of infusion.

Aprepitant after fosaprepitant administration

Following a single intravenous 150 mg dose of fosaprepitant administered as a 20-minute infusion to healthy adult volunteers, the mean $AUC_{0-\infty}$ of aprepitant was 35,0 µg·hr/ml and the mean maximal aprepitant concentration was 4,01 µg/ml.

Distribution

Aprepitant is highly protein bound, with a mean of 97 %. The geometric mean volume of distribution at steady state ($Vd_{ss}$) of aprepitant estimated from a single 150 mg intravenous dose of fosaprepitant is approximately 66 l in humans.

Biotransformation

Fosaprepitant was rapidly converted to aprepitant in *in vitro* incubations with liver preparations from humans. Furthermore, fosaprepitant underwent rapid and nearly complete conversion to aprepitant in S9 preparations from other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple tissues. In humans, fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion.

Aprepitant undergoes extensive metabolism.

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In healthy young adults, aprepitant accounts for approximately 24 % of the radioactivity in plasma over 72 hours following a single intravenous administration 100 mg dose of [$^{14}$C]-fosaprepitant, a prodrug for aprepitant, indicating a substantial presence of metabolites in the plasma. Twelve metabolites of aprepitant have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains and the resultant metabolites were only weakly active. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 and potentially with minor contribution by CYP1A2 and CYP2C19.

All metabolites observed in urine, faeces and plasma following an intravenous 100 mg [$^{14}$C]- fosaprepitant dose were also observed following an oral dose of [$^{14}$C]-aprepitant. Upon conversion of 245,3 mg of fosaprepitant dimeglumine (equivalent to 150 mg fosaprepitant) to aprepitant, 23,9 mg of phosphoric acid and 95,3 mg of meglumine are liberated.

Elimination

Aprepitant is not excreted unchanged in urine. Metabolites are excreted in urine and via biliary excretion in faeces. Following a single intravenously administered 100 mg dose of [$^{14}$C]- fosaprepitant to healthy subjects, 57 % of the radioactivity was recovered in urine and 45 % in faeces.

The pharmacokinetics of aprepitant is non-linear across the clinical dose range.

The terminal half-life of aprepitant following a 150 mg intravenous dose of fosaprepitant was approximately 11 hours. The geometric mean plasma clearance of aprepitant following a 150 mg intravenous dose of fosaprepitant was approximately 73 ml/min.

Pharmacokinetics in special populations

*Hepatic impairment:*

Fosaprepitant is metabolized in various extrahepatic tissues; therefore, hepatic impairment is not expected to alter the conversion of fosaprepitant to aprepitant. Mild hepatic impairment (Child-Pugh class A) does not affect the pharmacokinetics of aprepitant to a

clinically relevant extent. No dose adjustment is necessary for patients with mild hepatic impairment. Conclusions regarding the influence of moderate hepatic impairment (Child-Pugh class B) on aprepitant pharmacokinetics cannot be drawn from available data. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh class C).

*Renal impairment:*

A single 240 mg dose of oral aprepitant was administered to patients with severe renal impairment (CrCl < 30 ml/min) and to patients with end stage renal disease (ESRD) requiring haemodialysis.

In patients with severe renal impairment, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21 % and $C_{max}$ decreased by 32 %, relative to healthy subjects.

In patients with ESRD undergoing haemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42 % and $C_{max}$ decreased by 32 %. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound aprepitant was not significantly affected in patients with renal impairment compared with healthy subjects. Haemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0,2 % of the dose was recovered in the dialysate.

No dose adjustment is necessary for patients with renal impairment or for patients with ESRD undergoing haemodialysis.

*Paediatric population:*

As part of a 3-day IV/IV/IV regimen, simulated median $AUC_{0-24hr}$ of aprepitant with median peak plasma concentration ($C_{max}$ ) on Day 1 and the median concentrations at the end of day 1, Day 2 and Day 3 in paediatric patients (6 months to 17 years old) are shown in Table 7 below.

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**Table 7: Pharmacokinetic parameters of aprepitant for 3-day IV fosaprepitant regimen in paediatric patients**

| Population | 3-day IV/IV/IV dose | $AUC_{0-24hr}$ (ng*hr/ml) | $C_{max}$ (ng/ml) | $C_{24}$ (ng/ml) | $C_{48}$ (ng/ml) | $C_{72}$ (ng/ml) |
|---|---|---|---|---|---|---|
| 12-17 year old | 115 mg, 80 mg, 80 mg | 21172 | 2475 | 454 | 424 | 417 |
| 6 - <12 years old | 3 mg/kg, 2 mg/kg, 2 mg/kg | 25901 | 2719 | 518 | 438 | 418 |
| 2 - <6 years old | | 20568 | 2335 | 336 | 248 | 232 |
| 6 months - < 2 years old | | 16979 | 1916 | 256 | 179 | 167 |

In the 1-day IV fosaprepitant setting, simulated median $AUC_{0-24hr}$ of aprepitant with median peak plasma concentration ($C_{max}$) on Day 1 and the median concentrations at the end of Day 1, Day 2 and Day 3 in paediatric patients (6 months to < 12 years old) and observed mean $AUC_{0-24hr}$ with median peak plasma concentration ($C_{max}$) ) on Day 1 and mean concentrations at the end of Day 1, Day 2 and Day 3 in paediatric patients
(12 to 17 years old) are shown in Table 8.

**Table 8: Pharmacokinetic parameters of aprepitant for 1-day IV fosaprepitant regimen in paediatric patients**

| Population | 1-day IV/IV/IV dose | $AUC_{0-24hr}$ (ng*hr/ml) | $C_{max}$ (ng/ml) | $C_{24}$ (ng/ml) | $C_{48}$ (ng/ml) | $C_{72}$ (ng/ml) |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| 12-17 year old | 150 mg | 30400 | 3500 | 735 | NR* | NR* |
| 6 - <12 years old | 4 mg/kg | 35766 | 3637 | 746 | 227 | 69,2 |
| 2 - <6 years old | | 28655 | 3150 | 494 | 108 | 23,5 |
| 6 months - < 2 years old | 5 mg/kg | 30484 | 3191 | 522 | 112 | 24,4 |

*NR = Not reported

A population pharmacokinetic analysis of aprepitant in paediatric patients (aged 6 months through 17 years) suggests that gender and race have no clinically meaningful effect on the pharmacokinetics of aprepitant.

Relationship between concentration and effect

Positron emission tomography (PET) imaging studies, using a highly specific $NK_1$-receptor tracer, in healthy young men administered a single intravenous dose of 150 mg fosaprepitant (N = 8) demonstrated brain $NK_1$ receptor occupancy of ≥ 100 % at $T_{max}$, and 24 hours, ≥ 97 % at 48 hours, and between 41 % and 75 % at 120 hours, following dosing. Occupancy of brain $NK_1$ receptors, in this study, correlate well with aprepitant plasma concentrations.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium edetate

Polysorbate 80

Anhydrous lactose

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

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### 6.2 Incompatibilities

Fosaprepitant is incompatible with any solutions containing divalent cations (e.g., $Ca^{2+}$, $Mg^{2+}$), including Hartman's and lactated Ringer's solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

3 years

From a microbiological point of view, the medicinal 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 48 hours at 20 to 25 °C, unless reconstitution has taken place in controlled and validated aseptic.

Discard any unused portion.

### 6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

10 ml 13 mm clear flat bottom tubular glass vial with a grey siliconised rubber stopper and aluminium seal with orange coloured flip off plain top.

Pack sizes: 1 vial.

### 6.6 Special precautions for disposal and other handling

Fosaprepitant must be reconstituted and then diluted prior to administration.

Preparation of EMETEND 150 mg for intravenous administration:

1. Inject 5 ml saline into the vial. Assure that saline is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline into the vial. After reconstitution, use only if the solution is clear and free from visible particles.
2. Prepare an infusion bag filled with 145 ml of saline.
3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 ml of saline to yield a total volume of 150 ml. Gently invert the bag 2-3 times.

The medicinal product must not be reconstituted or mixed with solutions for which physical and chemical compatibility has not been established (see section 6.2).

The appearance of the reconstituted solution is the same as the appearance of the diluent.

The reconstituted and diluted medicinal product should be inspected visually for particulate matter and discoloration before administration.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

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South Africa

## 8. REGISTRATION NUMBER(S)

54/5.7.2/0865

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

20 September 2022

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## 10. DATE OF REVISION OF THE TEXT

To be confirmed