PROFESSIONAL INFORMATION FOR

FOSAPREPITANT CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FOSAPREPITANT CIPLA Lyophilised powder for Solution for Infusion.

Strength

Each 10 mL vial of FOSAPREPITANT CIPLA contains Fosaprepitant Dimeglumine 245,3 mg equivalent to Fosaprepitant 150 mg.

Pharmaceutical form

Lyophilised cake or powder for solution for Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial of FOSAPREPITANT CIPLA contains Fosaprepitant dimeglumine 245,3 mg equivalent to Fosaprepitant 150 mg.

When reconstituted (150 mg of Fosaprepitant in 150 mL 0,9 % Sodium chloride Injection), yields a final concentration of 1 mg/mL Fosaprepitant solution for infusion.

Contains Sugar (Lactose Anhydrous 375 mg).

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

3. PHARMACEUTICAL FORM

Lyophilised cake or powder for solution for Infusion.

Before Reconstitution: White to off white lyophilised cake or powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

FOSAPREPITANT CIPLA 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**.

4.2 Posology and method of administration

Posology

Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy is as follows:

Highly Emetogenic Chemotherapy Regimen				
	Day 1	Day 2	Day 3	Day 4
FOSAPREPITANT CIPLA	150 mg IV	None	None	None
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally, twice daily	8 mg orally, twice daily
5-HT_3 antagonist	See the professional information for the selected 5-HT_3 antagonist for appropriate dosing information	None	None	None

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 to 4. Dexamethasone should also be administered in the evenings on Days 3 and 4. The dose of dexamethasone accounts for active substance interactions.

Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Moderately Emetogenic Chemotherapy Regimen	
	Day 1
FOSAPREPITANT CIPLA	150 mg IV
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 active substance interactions

Method of administration

FOSAPREPITANT CIPLA is administered intravenously on Day 1, as an infusion over 20 to 30 minutes initiated approximately 30 minutes prior to chemotherapy. FOSAPREPITANT CIPLA should be administered in conjunction with a corticosteroid and a 5-HT_3 antagonist as specified in the tables above. The professional information for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with FOSAPREPITANT CIPLA.

Information on instructions for reconstitution and dilution of the medicine before administration, see **section 6.6**.

4.3. Contraindications

FOSAPREPITANT CIPLA is contraindicated:

- In patients who are hypersensitive to aprepitant, polysorbate 80 or any other ingredients of FOSAPREPITANT CIPLA.
- Pregnancy and breastfeeding, see **section 4.6.**
- In co-administration with pimozide, terfenadine, astemizole or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma

concentrations of these medicines, potentially causing serious life-threatening reactions, see **section 4.5**.

4.4. Special warnings and precautions for use

Severe hepatic insufficiency (Child-Pugh score > 9)

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency. Caution should be exercised when FOSAPREPITANT CIPLA is administered in these patients.

CYP3A4 interactions

FOSAPREPITANT CIPLA should be used with caution in patients receiving concomitant active substances that are metabolized 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.

Hypersensitivity reactions

Immediate hypersensitivity reactions including flushing, erythema, dyspnoea, and anaphylaxis/ anaphylactic shock have occurred during or soon after infusion of FOSAPREPITANT CIPLA. 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.

Administration and infusion site reactions

Infusion site reactions (ISRs) have been reported with the use of FOSAPREPITANT CIPLA, 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 without concomitant vesicant chemotherapy.

FOSAPREPITANT CIPLA 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 CIPLA 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.

Co-administration with warfarin (a CYP2C9 substrate)

Co-administration of FOSAPREPITANT CIPLA with warfarin may result in clinically significant decrease in the International Normalised Ratio (INR) or prothrombin time, In patients on chronic warfarin therapy, the INR should be monitored closely for the 2 week period, particularly at 7 to 10 days following initiation of FOSAPREPITANT CIPLA, see **section 4.5**.

Co-administration with hormonal contraceptives

The efficacy of hormonal contraceptives during and for 28 days after administration of FOSAPREPITANT CIPLA may be reduced. Alternative or non-hormonal back-up methods of contraception should be used during treatment with FOSAPREPITANT CIPLA and for 1 month following the last dose of FOSAPREPITANT CIPLA, see **section 4.5**.

Use in elderly

No dosage adjustment is necessary in elderly patients.

Lactose intolerance

FOSAPREPITANT CIPLA contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take FOSAPREPITANT CIPLA.

Paediatric Population

Safety and efficacy of FOSAPREPITANT CIPLA in paediatric patients have not been established, see **section 4.2**

4.5. Interaction with other medicines and other forms of interaction

When administered intravenously, Fosaprepitant is rapidly converted to aprepitant. Therefore, interactions following administration of FOSAPREPITANT CIPLA are likely to occur with medicines that interacts with oral aprepitant.

Aprepitant is a substrate, a weak to moderate inhibitor and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

FOSAPREPITANT CIPLA given as a single dose, is a weak inhibitor of CYP3A4, and thereby, may increase the plasma concentrations of co-administered medicines that are metabolised through CYP3A4. It does not induce CYP3A4. It is anticipated that FOSAPREPITANT CIPLA would cause less or no greater induction of CYP2C9 than that caused by the administration of oral aprepitant (see **Warfarin** and **Tolbutamide** below).

FOSAPREPITANT CIPLA 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**.

Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolised through CYP2C9. Co-administration of FOSAPREPITANT CIPLA with these

medicines or other medicines that are known to be metabolised by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these medicines.

FOSAPREPITANT CIPLA is unlikely to interact with medicines that are substrates for the P-glycoprotein transporter, due to the lack interaction of oral aprepitant with digoxin.

5-HT_3 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 FOSAPREPITANT CIPLA and 5-HT_3 antagonists.

Corticosteroids

Dexamethasone: FOSAPREPITANT CIPLA administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, a CYP3A4 substrate, by 2,0 fold on Days 1 and 2 when dexamethasone was co-administered as a single 8 mg oral dose on Days 1, 2, and 3. The oral dexamethasone dose on Days 1 and 2 should be reduced by approximately 50 % when co-administered with FOSAPREPITANT CIPLA on Day 1 to achieve exposure of dexamethasone similar to those obtained when given without FOSAPREPITANT CIPLA, see **section 4.2**.

Methylprednisolone: Oral aprepitant, when given as 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 at 125 mg on Day 1 and orally as 40 mg on Days 2 and 3.

Chemotherapeutic medicines

Caution and careful monitoring are advised in patients receiving etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan and paclitaxel or other chemotherapy medicines metabolised primarily by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide co-administration, see **section 4.4**.

Warfarin

In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the first two-week period particularly at 7 to 10 days, following initiation of the use of FOSAPREPITANT CIPLA with each chemotherapy cycle.
Prothrombin time (INR) should be done more frequently while using FOSAPREPITANT CIPLA.

Tolbutamide

Diabetic patients using tolbutamide should be monitored for glucose changes

Hormonal contraceptives

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of FOSAPREPITANT CIPLA. Alternative non-hormonal back-up methods of contraception should be used during treatment with FOSAPREPITANT CIPLA and for 1 month following the last dose of FOSAPREPITANT CIPLA.

Midazolam

FOSAPREPITANT CIPLA administered as a single intravenous dose on Day 1 increased the $AUC_{0-\infty}$ of midazolam by approximately 1,8-fold on Day 1 and had no effect (1,0-fold) on Day 4 when midazolam was co-administered as a single oral dose of 2 mg on Day 1 and 4.

FOSAPREPITANT CIPLA IV 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.

In addition, when FOSAPREPITANT CIPLA was administered as a dose of 100mg over 15 minutes along with a single dose of midazolam 2 mg, the plasma AUC of midazolam was increased by 1,6-fold. This effect was not considered clinically important.

Oral aprepitant increased the AUC of midazolam, by 2,3-fold on Day1 and 3,3-fold on Day 5, when a single oral dose of midazolam 2 mg was co-administered on Day 1 and Day 5 of a regimen of oral aprepitant 125 mg on Day 1 and 80 mg/day on Days 2 through 5.The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolised via CYP3A4 (alprazolam, triazolam) should be considered when co-administering these medicines with FOSAPREPITANT CIPLA.

Effect of other medicines on the pharmacokinetics of aprepitant

FOSAPREPITANT CIPLA should be used with caution in patients receiving concomitant medicines including chemotherapy medicines that are primarily metabolized through CYP3A4. Aprepitant is a substrate for CYP3A4, therefore, co-administration of FOSAPREPITANT CIPLA with medicines that inhibit CYP3A4 activity, may result in increased plasma concentration of aprepitant. Consequently, co-administration of FOSAPREPITANT CIPLA with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Because moderate CYP3A4 inhibitors (e.g. diltiazem) results in 2-fold increase in plasma concentration of aprepitant, concomitant administration should also be approached with caution.

Co-administration of FOSAPREPITANT CIPLA with medicines that strongly induce CYP3A4 activity (e.g. rifampicin, carbamazepine, phenytoin) may result in reduced plasma concentration of aprepitant that may result in decreased efficacy of FOSAPREPITANT CIPLA.

Concomitant administration of Fosaprepitant with herbal preparations containing St. John's Wort *(Hypericum perforatum)* is not recommended.

Ketoconazole

Concomitant administration of Fosaprepitant or aprepitant with strong CYP3A4 inhibitors should be approached cautiously.

Rifampicin

Concomitant administration of Fosaprepitant or aprepitant with medicines that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy.

Diltiazem

In patients with mild to moderate hypertension, infusion of FOSAPREPITANT CIPLA over 15 minutes with diltiazem 120 mg 3 times daily, may result in an increased diltiazem AUC and a meaningful decrease in blood pressure, with no clinically meaningful change in heart rate, or PR interval.

Paediatric population

Safety and efficacy of FOSAPREPITANT CIPLA in paediatric patients have not been established.

4.6. Fertility, pregnancy, and lactation

Women of childbearing potential / Contraception in males and females

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of FOSAPREPITANT CIPLA. Alternative or non-hormonal back-up methods of

contraception should be used during treatment with FOSAPREPITANT CIPLA and for 1 month following the last dose of FOSAPREPITANT CIPLA, see **section 4.4 and 4.5**.

Pregnancy

FOSAPREPITANT CIPLA is contraindicated in pregnancy, see **section 4.3**.

Breastfeeding

Mothers on treatment with FOSAPREPITANT CIPLA should not breastfeed their infants, as Breastfeeding is contraindicated during therapy with FOSAPREPITANT CIPLA, see **section 4.3**

4.7. Effects on ability to drive and use machines

FOSAPREPITANT CIPLA may cause side effects such as nausea dizziness which may affect the patient's ability to drive and use machines.

4.8. Undesirable effects

a) Summary of the safety profile

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

The frequency of occurrence of adverse events are described as follows:

Frequent: ‘more frequent’, ‘very common’ and ‘common’

Less Frequent: ‘single reports’ or ‘isolated reports’, ‘uncommon’, ‘rare’, ‘very rare’

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, alanine aminotransferase (ALT) increased, dyspepsia,

constipation, headache, and decreased appetite. 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.

The most common adverse reactions reported at a greater incidence in paediatric patients treated with the aprepitant regimen than with the control regimen while receiving emetogenic cancer chemotherapy were hiccups and flushing.

b) Tabulated list of adverse reactions - aprepitant

Below adverse reactions were observed in a pooled analysis of the HEC and MEC studies at a greater incidence with oral aprepitant than with standard therapy in adults or paediatric patients or in post-marketing use**.**

System Organ Class	**Frequency**	**Adverse reaction**
Infections and Infestations	*Less Frequent*	Candidiasis, staphylococcal infection
Blood and lymphatic system disorders	*Less Frequent*	Anaemia, febrile neutropenia
Immune system disorder	*Frequency not known*	Hypersensitivity reactions including anaphylactic reaction
Metabolism and nutrition disorders	*Frequent*	Decreased appetite
	Less Frequent	Polydipsia
Psychiatric disorders	*Less Frequent*	Anxiety, disorientation, euphoria
Nervous system disorders	*Frequent*	Headache
	Less Frequent	Dizziness, somnolence cognitive disorder, lethargy,

		dysgeusia
Eye disorders	*Less Frequent*	Conjunctivitis
Ear and labyrinth disorders	*Less Frequent*	Tinnitus
Cardiac disorders	*Less Frequent*	Palpitations, bradycardia, cardiovascular disorder
Vascular disorders	*Less Frequent*	Hot flushes
Respiratory, thoracic, and mediastinal disorders	*Frequent*	Hiccups
	Less Frequent	Oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation
Gastrointestinal disorders	*Frequent*	Constipation, dyspepsia
	Less Frequent	Eructation, nausea, vomiting, gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence duodenal ulcer perforation, stomatitis, abdominal distension, hard faeces, neutropenic colitis
Skin and subcutaneous tissue disorders	*Less Frequent*	Rash, acne, photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, pruritic rash, Stevens-Johnson syndrome/ toxic epidermal necrolysis, pruritus, urticaria
Musculoskeletal, connective tissue and bone disorders	*Less Frequent*	Muscular spasms, muscle weakness
Renal and urinary disorders	*Less frequent*	Dysuria, pollakiuria
General disorders and administration site conditions	*Frequent*	Fatigue
	Less Frequent	Asthenia, malaise, oedema, chest discomfort, gait disturbance

Investigations	*Frequent*	Increased ALT
	Less Frequent	Increased AST, increased blood alkaline phosphatase, increased urine output, positive red blood cells in urine, decreased blood sodium, decreased weight, glycosuria, decreased neutrophil count, presence of glucose in urine.

Tabulated list of adverse reactions – Fosaprepitant

The following additional clinically important medicine-related adverse reactions occurred with Fosaprepitant 150 mg and have not been reported in earlier with oral aprepitant as described above.

System Organ Class	Frequency	Adverse reaction
Vascular disorders	*Less Frequent*	Flushing, thrombophlebitis (predominantly, infusion-site thrombophlebitis)
Skin and subcutaneous tissue disorders	*Less Frequent*	Erythema
General disorders and administration site conditions	*Less Frequent*	Infusion site erythema, infusion site pain, infusion site pruritus, infusion site induration, immediate hypersensitivity reactions including flushing, erythema, dyspnoea, anaphylactic reactions/ anaphylactic shock
Investigations	*Frequent*	Increased blood pressure

c) Description of selected adverse reactions

Additional adverse reactions were observed in adult patients treated with aprepitant for post-operative nausea and vomiting (PONV) and a greater incidence than with ondansetron: abdominal pain upper, bowel sounds abnormal, constipation*, dysarthria, dyspnoea,

hypoesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, sub-ileus*, visual acuity reduced, wheezing.

*Reported in patients taking a higher dose of aprepitant.

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 the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9. Overdose

In the event of overdose, FOSAPREPITANT CIPLA should be discontinued and general supportive treatment and monitoring should be provided.

Aprepitant cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.2 Anti-emetics and antivertigo preparations

Pharmacotherapeutic group: Antiemetics and antinauseants

ATC code: A04AD12

Fosaprepitant dimeglumine is the prodrug of aprepitant. When administered intravenously, it is converted to aprepitant, a substance P neurokinin 1 (NK_1) receptors antagonist.

Its anti-emetic effects are attributed to aprepitant.

NK_1-receptors antagonist inhibits emesis induced by cytotoxic chemotherapeutic medicines, such as cisplatin, via central actions. Aprepitant studies have shown that it penetrates the brain and occupies brain NK_1-receptors.

5.2. Pharmacokinetic properties

Following a single intravenous 150 mg dose of Fosaprepitant administered as a 20-minute infusion to healthy 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.

The aprepitant terminal half-life ranged from approximately 9 to 13 hours.

Fosaprepitant is rapidly converted to aprepitant.

Aprepitant is > 95 % bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (Vd_{ss}) is approximately 66 litres in humans.

Aprepitant crosses the placenta and blood brain barrier.

Biotransformation

In humans, Fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion. Fosaprepitant undergoes rapid and nearly complete conversion to aprepitant in the liver and other extra-hepatic human tissues including kidney, lung, and ileum.

Aprepitant undergoes further extensive metabolism. In healthy young adults aprepitant accounts for approximately 24 % of the radioactivity in plasma over 72 hours following a single oral 300 mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant which are only weakly active, have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised

primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9 or CYP2E1.

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

Elimination

Following administration of a single IV 100 mg dose of [^{14}C]-aprepitant to healthy subjects, 57 % of the radioactivity was recovered in urine and 45 % in faeces.

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted.

Elderly

Following oral administration of a single 125 mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{0\text{-}24hr}$ of aprepitant was 21 % higher on Day 1 and 36 % higher on Day 5 in elderly (65 years and older) relative to younger adults, The C_{max} was 10 % higher on Day 1 and 24 % higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment Is necessary In elderly patients.

Hepatic insufficiency

Fosaprepitant is metabolised in various extra-hepatic tissues; therefore, hepatic insufficiency is not expected to alter the conversion of Fosaprepitant to aprepitant.

Oral aprepitant was well tolerated in patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic insufficiency. The pharmacokinetic changes are not

considered clinically meaningful; therefore, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9), see **section 4.4**.

Renal insufficiency

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

In patients with severe renal insufficiency, 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 insufficiency compared with healthy subjects. Haemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; < 0,2 % of the dose was recovered in the dialysate.

No dosage adjustment is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing haemodialysis.

Paediatric population

Fosaprepitant has not been evaluated in patients below 18 years of age.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Disodium edetate

Hydrochloric acid

Lactose Anhydrous

Polysorbate - 80

Sodium hydroxide pellets

Water for Injection

Contains sugar (Lactose Anhydrous 375 mg).

6.2. Incompatibilities

FOSAPREPITANT CIPLA is incompatible with any solutions containing divalent cations (e.g. Ca^{2+}, Mg^{2+}), including Hartman's and lactated Ringer's solutions. FOSAPREPITANT CIPLA must not be reconstituted or mixed with solutions for which physical and chemical compatibility have not been established.

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

6.3 Shelf Life

24 months

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C.

From a microbiological point of view, FOSAPREPITANT CIPLA 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 25 °C.

6.4 Special precautions for storage

Store in refrigerator (2 °C to 8 °C).

For storage conditions after reconstitution and dilution of the FOSAPREPITANT CIPLA, see **section 6.3**

6.5 Nature and contents of container

FOSAPREPITANT CIPLA is packed in 10 mL clear tubular Type I glass vial, with 13 mm grey bromobutyl double slotted rubber stopper and sealed with aluminium flip-off seal with green colour polypropylene disc.

1 or 10 Vials are further packed in a printed carton along with instructions for use.

6.6 Special precautions for disposal and other handling

Preparation of FOSAPREPITANT CIPLA for injection

1. After reconstitution FOSAPREPITANT CIPLA is a clear colourless to pale yellow colour solution free from visible particle matter.
2. Aseptically inject 5 mL 0,9 % Sodium chloride injection, into the vial. Assure that 0,9 % sodium chloride injection is added to the vial along the vial wall to prevent foaming. Swirl the vial gently, avoid shaking and jetting 0,9 % Sodium chloride injection into the vial. After reconstitution, use only if solution is a clear colourless to pale yellow colour solution free from visible particle matter.
3. Aseptically prepare an infusion bag filled with 145 mL of 0,9 % Sodium chloride injection,
4. Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing 145 mL of 0,9 % Sodium chloride injection, to yield a total volume of 150 mL and a final concentration of 1 mg/mL.
5. Gently invert the bag 2 to 3 times

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

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Parc du Cap

Mispel Street

Bellville

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Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

55/5.7.2/0452

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 February 2023

10. DATE OF REVISION OF THE TEXT