PROFESSIONAL INFORMATION FOR

APREPITANT CIPLA (capsule)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

APREPITANT 80 CIPLA (80 mg Capsules)

APREPITANT 125 CIPLA (125 mg Capsules)

APREPITANT COMBI PACK CIPLA (125 mg and 80 mg Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each APREPITANT 80 CIPLA (80 mg capsule) contains 80 mg aprepitant.

Each APREPITANT 125 CIPLA (125 mg capsule) contains 125 mg aprepitant.

Each APREPITANT 80 CIPLA (80 mg capsule) contains 80 mg sucrose.

APREPITANT 125 CIPLA (125 mg capsule) contains 125 mg sucrose.

Each APREPITANT 80 CIPLA (80 mg capsule) contains 0,0610 mg sodium lauryl sulfate.

APREPITANT 125 CIPLA (125 mg capsule) contains 0,0760 mg sodium lauryl sulfate.

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

3. PHARMACEUTICAL FORM

APREPITANT 80 CIPLA (80 mg capsules): Opaque size 2 hard gelatin capsules with a white cap and white body, printed with “80 mg” on the body.

APREPITANT 125 CIPLA (125 mg capsules): Opaque size 1 hard gelatin capsules with a pink cap and white body, printed with “125 mg” on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APREPITANT CIPLA, in combination with other antiemetic medicines, is indicated for the prevention of acute and delayed 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

APREPITANT CIPLA is given for 3 days as part of a regimen that includes a corticosteroid for 4 days and a 5-HT_3 antagonist on day one. The professional information for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with APREPITANT CIPLA. The recommended dose of APREPITANT CIPLA is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.

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

	Day 1	Day 2	Day 3	Day 4

APREPITANT CIPLA	125 mg	80 mg	80 mg	None
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
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 through 4. The dose of dexamethasone was chosen to account for medicine interactions.

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

	Day 1	Day 2	Day 3
APREPITANT CIPLA	125 mg	80 mg	80 mg
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally
5-HT_3 antagonist	See the professional information for the selected 5-HT_3 antagonist for appropriate dosing	None	None

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

1. **The dose of dexamethasone accounts for interactions.**

See **section 4.5** for additional information on the administration of APREPITANT CIPLA with corticosteroids.

Refer to the full prescribing information for co-administered anti-emetic medicines.

Special populations

No dosage adjustment is necessary based on age, gender, race or Body Mass Index (BMI).

Renal impairment:

No dosage adjustment is necessary for patients with severe renal insufficiency (creatinine clearance < 30 mL/min) or for patients with end stage renal disease undergoing hemodialysis.

Hepatic impairment:

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).

Elderly population:

No dosage adjustment is necessary for the elderly.

Paediatric population

Safety and effectiveness in paediatric patients have not been established.

Method of administration

The hard capsule should be swallowed whole.

APREPITANT CIPLA may be taken with or without food.

4.3 Contraindications

APREPITANT CIPLA is contraindicated in patients who are hypersensitive to aprepitant or to any of the excipients (see **section 6.1**).

APREPITANT CIPLA should not be used concurrently 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 or life-threatening reactions (see **section 4.5**).

Safety and effectiveness of APREPITANT CIPLA in paediatric patients have not been established.

4.4 Special warnings and precautions for use

CYP3A4 inhibition

APREPITANT CIPLA should be used with caution in patients receiving concomitant medicines that are primarily metabolized through CYP3A4; some chemotherapy medicines are metabolized by CYP3A4 (see **section 4.5**). Inhibition of CYP3A4 by aprepitant may result in elevated plasma concentrations of these concomitant medicines (see **section 4.5**). Consequently, concomitant administration of

APREPITANT CIPLA with strong CYP3A4 inhibitors (itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir) should be approached with caution. Similarly, APREPITANT CIPLA should be used with caution with medicines with a narrow therapeutic range, such as ciclosporin, tacrolimus, sirolimus, everolimus, alfentanil, ergot alkaloid derivatives, fentanyl and quinidine (see **section 4.5**). Concomitant administration with irinotecan should also be approached with caution, as the combination may result 120 in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)

Co-administration of APREPITANT CIPLA with warfarin may result in decreased prothrombin time, reported as International Normalized Ratio (INR). In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7-10 days to establish and maintain the required dose of warfarin, after completion of the 3-day regimen of APREPITANT CIPLA with each chemotherapy cycle (see **section 4.5**)

Co-administration with hormonal contraceptives

The efficacy of hormonal contraceptives during and for 28 days after administration of APREPITANT CIPLA may be reduced. Alternative or back-up methods of contraception should be used during treatment with PRODUCT NAME and for 1 month following the last dose of APREPITANT CIPLA (see **section 4.5**). Alternative nonhormonal back up methods of contraception should be used during treatment with APREPITANT CIPLA and for 2 months following the last dose of APREPITANT CIPLA.

Severe hepatic insufficiency

Patients with 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 APREPITANT CIPLA is administered in these patients.

Use in elderly

In clinical studies, the efficacy and safety of APREPITANT CIPLA in the elderly (65 years and older) were comparable to those seen in younger patients (younger than 65 years). No dosage adjustment is necessary in elderly patients.

Excipients

APREPITANT CIPLA contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take APREPITANT CIPLA.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicines and other forms of interaction

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with aprepitant, as in APREPITANT CIPLA, CYP3A4 is inhibited. After the end of treatment, APREPITANT CIPLA causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation. Aprepitant does

not seem to interact with the P-glycoprotein transporter, as suggested by the lack of interaction of aprepitant with digoxin.

Effect of APREPITANT CIPLA capsules on the pharmacokinetics of other medicines:

CYP3A4 inhibition

As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of co-administered medicines that are metabolised through CYP3A4. The total exposure of orally administered CYP3A4 substrates may increase up to approximately 3-fold during the 3-day treatment with aprepitant; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller.

APREPITANT CIPLA should not be used concurrently with pimozide, terfenadine, astemizole or cisapride. Inhibition of CYP3A4 by APREPITANT CIPLA could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see **section 4.3**). Caution is advised during concomitant administration of APREPITANT CIPLA and orally administered 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**).

5-HT-3 antagonists

In clinical studies, APREPITANT CIPLA did not have any effects on the pharmacokinetics of ondansetron, granisetron or hydrodolasetron (the active metabolite of dolasetron).

Corticosteroids

Dexamethasone: APREPITANT CIPLA when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and APREPITANT CIPLA when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate by 2,2-fold, on Days 1 and 5. The usual oral dexamethasone doses should be reduced by approximately 50 % when co-administered with APREPITANT CIPLA, to achieve exposures of dexamethasone similar to those obtained when it is given without APREPITANT CIPLA. The daily dose of dexamethasone administered in clinical studies with APREPITANT CIPLA reflects an approximate 50 % reduction of the dose of dexamethasone (see **section 4.2**)

Methylprednisolone

APREPITANT CIPLA, 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. The usual IV methylprednisolone dose should be reduced by approximately 25 %, and the usual oral methylprednisolone dose should be reduced by approximately 50 % when co-administered with APREPITANT CIPLA, to achieve exposures of

methylprednisolone similar to those obtained when it is given without APREPITANT CIPLA. During continuous treatment with methylprednisolone, the AUC of methylprednisolone may decrease at later time points within 2 weeks following initiation of the aprepitant as in APREPITANT CIPLA dose, due to the inducing effect of aprepitant on CYP3A4. This effect may be expected to be more pronounced for orally administered methylprednisolone.

Chemotherapeutic medicines

In clinical studies, aprepitant was administered with the following chemotherapeutic medicines metabolised primarily or in part by CYP3A4: Etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan and paclitaxel. The doses of these medicines were not adjusted to account for potential medicine interactions. Caution and careful monitoring are advised in patients receiving these medicines or other chemotherapy medicines metabolised primarily by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported if APREPITANT CIPLA and ifosfamide are co-administered (see **section 4.4**).

Docetaxel

APREPITANT CIPLA may not influence the pharmacokinetics of docetaxel.

Warfarin

A single 125 mg dose of APREPITANT CIPLA was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilised on chronic warfarin therapy. Although there was no effect of APREPITANT CIPLA on the plasma AUC of

R(+) or S(-) warfarin determined on Day 3, there was a 34 % decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14 % decrease in the prothrombin time (reported as International Normalised Ratio or INR) 5 days after completion of dosing with APREPITANT CIPLA. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days following initiation of the 3-day regimen of APREPITANT CIPLA with each chemotherapy cycle.

Co-administration of APREPITANT 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.

APREPITANT CIPLA is unlikely to interact with medicines that are substrates for the P-glycoprotein transporter.

Tolbutamide

APREPITANT CIPLA, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23 % on Day 4, 28 % on Day 8, and 15 % on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of APREPITANT CIPLA and on Days 4, 8 and 15.

Hormonal contraceptives

APREPITANT CIPLA, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 meg of ethinylestradiol and 1 mg of norethindrone,

decreased the AUC of ethinylestradiol by 43 %, and decreased the AUC of norethindrone by 8 %.

In another study, a single dose of an oral contraceptive containing ethinylestradiol and norethindrone was administered on Days 1 through 21 with APREPITANT CIPLA, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day Band 8 mg/day on Days 9, 10 and 11. In the study, the AUC of ethinylestradiol decreased by 19 % on Day 10 and there was as much as a 64 % decrease in ethinylestradiol trough concentrations during Days 9 through 21. While there was no effect of APREPITANT CIPLA on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21.

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

Midazolam

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 APREPITANT CIPLA (125 mg/ 80 mg).

Aprepitant capsules increased the AUC of midazolam, a sensitive CYP3A4 substrate, 2,3 fold on Day 1 and 3, 3 fold on Day 5, when a single oral dose of 2 mg midazolam was co-administered on Days 1 and 5 of a regimen of aprepitant capsules 125 mg on Day 1 and 80 mg/day on Days 2 to 5.

In another study with intravenous administration of midazolam, aprepitant capsules was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and 2 mg midazolam was given intravenously prior to the administration of the 3 day regimen of aprepitant capsules and on Days 4, 8 and 15. Aprepitant capsules increased the AUC of midazolam 25 % on Day 4 and decreased the AUC of midazolam 19 % on Day 8 and 4 % on Day 15. These effects were not considered clinically important.

In a third study with intravenous and oral administration of midazolam, aprepitant capsules was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, together with ondansetron 32 mg Day 1, dexamethasone 12 mg Day 1 and 8 mg Days 2 4. This combination (i.e. aprepitant capsules, ondansetron and dexamethasone) decreased the AUC of oral midazolam 16 % on Day 6, 9 % on Day 8, 7 % on Day 15 and 17 % on Day 22. These effects were not considered clinically important.

An additional study was completed with intravenous administration of midazolam and aprepitant capsules. Intravenous 2 mg midazolam was given 1 hour after oral administration of a single dose of aprepitant capsules 125 mg. The plasma AUC of midazolam was increased by 1,5 fold. This effect was not considered clinically important.

Induction

As a mild inducer of CYP2C9, CYP3A4 and glucuronidation, aprepitant can decrease plasma concentrations of substrates eliminated by these routes within two weeks following initiation and treatment. This effect may become apparent only after the end of a 3 day treatment with APREPITANT CIPLA. For CYP2C9 and CYP3A4 substrates, the induction is transient with a maximum effect reached 3 5 days after end of the APREPITANT CIPLA 3 day treatment. The effect is maintained for a few days, thereafter slowly declines and is clinically insignificant by two weeks after end of APREPITANT CIPLA treatment. Mild induction of glucuronidation is also seen with 80 mg oral aprepitant given for 7 days. Data are lacking regarding effects on CYP2C8 and CYP2C19. Caution is advised when warfarin, acenocoumarin, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered during this time period.

Effect of other medicines on the pharmacokinetics of aprepitant:

APREPITANT CIPLA should be used with caution in patients receiving concomitant medicinal products, including chemotherapy medicines that are primarily metabolised through CYP3A4.

APREPITANT CIPLA is a substrate for CYP3A4; therefore, co-administration of APREPITANT CIPLA with medicines that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of APREPITANT 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) result in a 2-fold increase in plasma concentrations of aprepitant,

concomitant administration should also be approached with caution. APREPITANT CIPLA is a substrate for CYP3A4; therefore, co-administration of APREPITANT CIPLA with medicines that strongly induce CYP3A4 activity (e.g., rifampin, carbamazepine, phenytoin) may result in reduced plasma concentrations of APREPITANT CIPLA that may result in decreased efficacy of APREPITANT CIPLA.

Ketoconazole

When a single 125 mg dose of APREPITANT CIPLA was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of APREPITANT CIPLA increased approximately 5-fold and the mean terminal half-life of APREPITANT CIPLA increased approximately 3-fold. Concomitant administration of APREPITANT CIPLA with strong CYP3A4 inhibitors should be approached cautiously.

Rifampicin

When a single 375 mg dose of APREPITANT CIPLA was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampicin, a strong CYP3A4 inducer, the AUC of APREPITANT CIPLA decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold. Co-administration of APREPITANT CIPLA with medicines that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of APREPITANT CIPLA.

Diltiazem

In patients with mild to moderate hypertension, administration of APREPITANT CIPLA once daily, as a tablet formulation comparable to 230 mg of the capsule formulation,

with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of APREPITANT CIPLA AUC and a simultaneous 1,7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate, or blood pressure beyond those changes induced by diltiazem alone.

Paroxetine

Co-administration of once daily doses of APREPITANT CIPLA, 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 CIPLA and paroxetine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy of APREPITANT CIPLA in pregnancy has not been established, as there are no adequate and well-controlled studies in pregnant women.

Breastfeeding

Women breastfeeding their infants should not use APREPITANT CIPLA. Aprepitant is excreted in the milk of lactating rats. It is not known whether APREPITANT CIPLA is excreted in human milk. Mothers on APREPITANT CIPLA should not breastfeed their babies.

Fertility

The potential for effects of aprepitant on fertility has not been fully characterized 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 (see **section 5.3**).

4.7 Effects on ability to drive and use machines

APREPITANT CIPLA may have minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of APREPITANT CIPLA (see **section 4.8**)

4.8 Undesirable effects

Summary of the safety profile

The overall safety of aprepitant capsules was evaluated in approximately 6 500 individuals.

Highly Emetogenic Chemotherapy (HEC)

In 2 clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), aprepitant capsules were given in combination with ondansetron and dexamethasone (aprepitant regimen) and compared with ondansetron and dexamethasone alone.

The most common aprepitant-related adverse experiences reported in patients treated with the aprepitant regimen and greater than the comparator therapy were: Hiccups (4,6 %), increased alanine aminotransferase (ALT) (2,8 %), dyspepsia (2,4 %), constipation (2,4 %), headache (2,0 %) and decreased appetite (2,0 %).

Moderately Emetogenic Chemotherapy (MEC)

In 2 clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), aprepitant capsules was given in combination with ondansetron and dexamethasone (aprepitant regimen).

In Cycle 1, aprepitant-related adverse experiences were reported in 14 % of patients treated with the aprepitant regimen. Aprepitant capsules was discontinued due to aprepitant-related adverse experiences in 0,7 % patients treated with the aprepitant regimen.

The most common aprepitant-related adverse experience reported at a greater incidence with the aprepitant regimen than with standard therapy was fatigue (1,4 %).

Highly and Moderately Emetogenic Chemotherapy

The following medicine-related adverse experiences were observed in patients treated with the APREPITANT CIPLA regimen and at a greater incidence than treatment with ondansetron and dexamethasone therapy.

Infection and infestations

Less frequent: Candidiasis, staphylococcal infection

Blood and the lymphatic system disorders

Less frequent: Anaemia, febrile neutropenia

Immune system disorder

Frequency unknown: Hypersensitivity reactions including anaphylactic reactions

Metabolism and nutrition disorders

Frequent: Decreased appetite

Less frequent: Polydipsia

Psychiatric disorders

Less frequent: Anxiety, disorientation, euphoric mood

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/flushing

Respiratory, thoracic and mediastinal disorders

Frequent: Hiccups

Less frequent: Oropharyngeal pain, sneezing, cough, post-nasal drip, throat irritation

Gastrointestinal disorders

Frequent: Dyspepsia, constipation

Less frequent: Eructation, nausea, gastroesophageal reflux disease, vomiting, 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

Frequency unknown: Urticaria, prutitus

Musculoskeletal and connective tissue disorders

Less frequent: Muscle 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 alanine aminotransferase (ALT)

Less frequent: Increased aspartate transaminase (AST), increased blood alkaline phosphatase, Increased urine output, positive red blood cells urine, decreased blood sodium, decreased weight, glucose urine present, decreased neutrophil count

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 by e-mail: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free). In addition, report any suspected adverse reactions to SAHPRA via “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No specific information is available on the treatment of overdosage with APREPITANT CIPLA

Drowsiness and headache were reported in one patient who ingested 1 440 mg of APREPITANT CIPLA. In the event of overdose, APREPITANT CIPLA should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, emesis induced by a medicine may not be effective.

APREPITANT CIPLA cannot be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

APREPITANT CIPLA (aprepitant) is a substance P neurokinin 1 (NK1) receptor antagonist.

Aprepitant is a selective high affinity antagonist at human substance P neurokinin 1 (NK1) receptors. Counter-screening assays showed that aprepitant was at least 3 000-fold selective for the NK1 receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing Chemotherapy Induced Nausea and Vomiting (CINV) therapies.

NK1-receptor antagonists have been shown pre-clinically to inhibit emesis induced by cytotoxic chemotherapeutic medicines, such as cisplatin, via central actions. Pre-clinical and human Positron Emission Tomography (PET) studies with aprepitant have shown that it is brain penetrant and occupies brain NK1 receptors. Pre-clinical studies show that aprepitant has a long duration of central activity, inhibits both the acute and delayed phases of cisplatin-induced emesis, and augments the anti-emetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

5.2 Pharmacokinetic properties

Absorption:

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65 % and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4

hours (T_{max}). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26 % greater than dose proportional between 80 mg and 125 mg single doses administered in the fed state.

Following oral administration of a single 125 mg dose of a product containing aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24hr} was approximately 19,5 mcg•hr/mL and 20,1 mcg•hr/mL on Day 1 and Day 3, respectively. The C_{max} of 1,5 mcg/mL and 1,4 mcg/mL were reached in approximately 4 hours (T_{max}) on Day 1 and Day 3, respectively.

Distribution:

Aprepitant is > 95 % bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (V_{dss}) is approximately 66 litres in humans.
Aprepitant crosses the placenta in rats, and crosses the blood brain barrier in rats and ferrets. PET studies in humans indicate that aprepitant crosses the blood brain barrier (see **section 5.1**)

Biotransformation:

Aprepitant undergoes 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.

Elimination:

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. Following administration of a single oral 300 mg dose of [14C]-aprepitant to healthy subjects, 5 % of the radioactivity was recovered in urine and 86 % in faeces. The apparent plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Gender

Following oral administration of a single 125 mg dose of APREPITANT CIPLA, the $AUC_{0\text{-}24hr}$ and C_{max} for aprepitant are 9 % and 17 % higher, respectively, in females as compared with males. The half-life of aprepitant is approximately 25 % lower in females as compared with males and its T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Elderly

Following oral administration of a single 125 mg dose of APREPITANT CIPLA 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 for APREPITANT CIPLA is necessary in elderly patients.

Paediatric

The pharmacokinetics of APREPITANT CIPLA have not been evaluated in patients below 18 years of age.

Hepatic insufficiency

APREPITANT CIPLA was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125 mg dose of APREPITANT CIPLA on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the AUC_{0-24hr} of aprepitant was 11 % lower on Day 1 and 36 % lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the AUC_{0-24hr} of aprepitant was 10 % higher on Day 1 and 18 % higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC0-24hr are not considered clinically meaningful; therefore, no dosage adjustment for APREPITANT CIPLA 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).

Renal insufficiency

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

In patients with severe renal insufficiency, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21 % and Cmax 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 medicine 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 for APREPITANT CIPLA is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APREPITANT CIPLA

Hypromellose 2910

Poloxamer 407

Sucrose

Microcrystalline cellulose

Capsule shell:

Gelatin

Sodium lauryl sulfate

Titanium dioxide E171

Iron oxide Red E172 (For 125 mg capsule only)

Shellac

Iron oxide black E172

Propylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

APREPITANT COMBI PACK CIPLA (80 mg and 125 mg capsules) are packed in a cardboard box containing OPA/ALU/PVC -Aluminium foil blisters containing 5 capsules.

APREPITANT 125 CIPLA (125 mg capsules) are packed in a cardboard box containing OPA/ALU/PVC -Aluminium foil blisters containing 5 capsules.

APREPITANT COMBI PACK CIPLA (80 mg and 125 mg capsules) is packed in a cardboard box containing OPA/ALU/PVC -Aluminium foil blisters containing one 125 mg capsule and two 80 mg capsules.

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage or disposal conditions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9, Parc du Cap,

Mispel Street,

Belville, 7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

52/5.7.2/0578

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 May 2022

10. DATE OF REVISION OF THE TEXT

14 April 2022