APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VOPREP 80 hard capsules

VOPREP 125 hard capsules

VOPREP Combi Pack hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 80 mg capsule contains 80 mg aprepitant.

Each 125 mg capsule contains 125 mg aprepitant.

Contains sugar:

Each 80 mg capsule contains 80 mg sucrose.

Each 125 mg capsule contains 125 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

The 80 mg capsules are opaque hard gelatine capsule with a white cap and white body printed with ‘80mg’ on the body.

The 125 mg capsules are opaque hard gelatine capsule with a pink cap and white body, printed with ‘125mg’ on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VOPREP in combination with other anti-emetic 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

VOPREP 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 referred to prior to the initiation of treatment with [PRODUCT NAME].

The recommended dose of VOPREP is 125 mg orally 1 hour prior to chemotherapy (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**
[PRODUCT NAME]	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-	None	None	None

	HT_3 antagonist for appropriate dosing information			

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

*** See the professional information for the selected 5-HT_3 antagonist for appropriate dosing information.

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

	Day 1	**Day 2**	**Day 3**
[PRODUCT NAME]	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 information	None	None

** Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for interactions.

*** See the professional information for the selected 5-HT_3 antagonist for appropriate dosing information.

See section 4.5 for additional information on the administration of VOPREP with corticosteroids.

Refer to the professional 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 haemodialysis.

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).

Method of administration

For oral use VOPREP can be taken with or without food.

4.3 Contraindications

Hypersensitivity to aprepitant or to any of the inactive ingredients of VOPREP (see section 6.1).

VOPREP should not be used concurrently with pimozide, terfenadine, astemizole or cisapride. Inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by VOPREP could result in elevated plasma concentrations of these medicines, potentially causing serious or life-threatening reactions (see section 4.5).

Paediatric use:

The safety and efficacy of VOPREP in paediatric patients have not been established.

4.4 Special warnings and precautions for use

Patients with severe hepatic impairment

There are and no data in patients with severe hepatic impairment. VOPREP should be used with caution in these patients (see section 5.2).

CYP3A4 interactions

VOPREP should be used with caution in patients receiving concomitant orally administered 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 caution as the combination might result in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)

Co-administration of VOPREP with warfarin may result in a clinically significant decrease in international normalised ratio (INR) or prothrombin time. In patients on chronic warfarin therapy, the INR should be monitored closely during treatment with VOPREP and for 14 days following each 3-day course of VOPREP (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 [PRODUCT NAME]. Alternative non-hormonal back-up methods of contraception should be used during treatment with VOPREP and for 1 month following the last dose of VOPREP (see section 4.5).

Use in the elderly

The efficacy and safety of **VOPREP** in the elderly (65 years and older) were comparable to those seen in younger patients (< 65 years). No dosage adjustment is necessary in elderly patients.

Sucrose

VOPREP capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take [PRODUCT NAME].

4.5 Interaction with other medicines and other forms of interaction

Effect of aprepitant on the pharmacokinetics of other medicines

Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with [PRODUCT NAME], CYP3A4 is inhibited. After the end of treatment, VOPREP 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.

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 [PRODUCT NAME]; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. VOPREP must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride (see section 4.3). Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. Caution is advised during concomitant administration of VOPREP and orally administered active substances that are metabolised primarily through CYP3A4 and with a narrow therapeutic range, such as cyclosporine, tacrolimus, sirolimus, everolimus, alfentanil, diergotamine, ergotamine, fentanyl, and quinidine (see section 4.4).

Corticosteroids:

Dexamethasone: VOPREP when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and VOPREP 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, 2,2-fold on Days 1 and 5. The usual oral dexamethasone dose should be reduced by approximately 50 % when co-administered with VOPREP to achieve exposures of dexamethasone similar to those obtained when it is given without [PRODUCT NAME]. The daily dose of dexamethasone administered in clinical studies with VOPREP reflects an approximate 50 % reduction of the dose of dexamethasone (see section 4.2).

Methylprednisolone: VOPREP 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 intravenously administered methylprednisolone dose should be reduced by approximately 25 %, and the usual oral methylprednisolone dose should be reduced approximately 50 % when co-administered with [PRODUCT NAME], to achieve exposures of methylprednisolone similar to those obtained when it is given without [PRODUCT NAME].

During continuous treatment with methylprednisolone, the AUC of methylprednisolone may decrease at later time points within 2 weeks following initiation of the VOPREP dose, due to the inducing effect of VOPREP 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 (e.g. etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan and paclitaxel). The doses of these medicines were not adjusted to account for potential medicine interactions. Caution is advised and additional monitoring may be appropriate in patients receiving medicines metabolised 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 co-administration.

Immunosuppressants

During the 3-day CINV regimen, a transient moderate increase followed by a mild decrease in exposure of immunosuppressants metabolised by CYP3A4 (e.g., cyclosporine, tacrolimus, everolimus and sirolimus) is expected.

Given the short duration of the 3-day regimen and the time-dependent limited changes in exposure, dose reduction of the immunosuppressant is not recommended during the 3 days of co-administration with [PRODUCT NAME].

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 [PRODUCT NAME].

VOPREP 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 VOPREP 125 mg on Day 1 and 80 mg/day on Days 2 to 5.

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 [PRODUCT NAME]. For CYP2C9 and CYP3A4 substrates, the induction is transient with a maximum effect reached 3 – 5 days after end of the VOPREP 3-day treatment. The effect is maintained for a few days, thereafter slowly declines and is clinically insignificant by two weeks after end of VOPREP 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, acenocoumarol, tolbutamide, phenytoin or other active substances that are known to be metabolised by CYP2C9 are administered during this period.

Warfarin

In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days following initiation of the 3-day regimen of VOPREP with each chemotherapy cycle.

A single 125 mg dose of VOPREP was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy individuals who were stabilised on chronic warfarin therapy. Although there was no effect of VOPREP 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 INR 5 days after completion of treatment with [PRODUCT NAME].

Tolbutamide

VOPREP 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 VOPREP and on Days 4, 8, and 15.

Hormonal contraceptives

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of [PRODUCT NAME]. Alternative non-hormonal back-up methods of contraception should be used during treatment with VOPREP and for 2 months following the last dose of [PRODUCT NAME].

5-HT_3 antagonists

VOPREP did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).

Effect of other medicines on the pharmacokinetics of aprepitant

Concomitant administration of VOPREP with medicines that inhibit CYP3A4 activity (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, troleandomycin, telithromycin, nefazodone and protease inhibitors) should be approached cautiously, as the combination is expected to result in several-fold in increased plasma concentrations of VOPREP (see section 4.4).

Concomitant administration of VOPREP with active substances that strongly induce CYP3A4 activity (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitone) should be avoided as

the combination results in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy of [PRODUCT NAME].

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

Ketoconazole

When a single 125 mg dose of VOPREP was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of VOPREP increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold.

Rifampicin

When a single 375 mg dose of VOPREP was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampicin, a strong CYP3A4 inducer, the AUC of aprepitant decreased 91 % and the mean terminal half-life decreased 68 %.

Additional interactions

Diltiazem

In patients with mild to moderate hypertension, administration of VOPREP once daily with 120 mg diltiazem 3 times daily for 5 days, resulted in a 2-fold increase of VOPREP AUC and a simultaneous 1,7-fold increase of diltiazem AUC. These 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 VOPREP with 20 mg paroxetine once daily resulted in a decrease in AUC by approximately 25 % and C_{max} by approximately 20 % of both

VOPREP and paroxetine.

Paediatric population

Interaction study in paediatric population is not known

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 [PRODUCT NAME].

Alternative non-hormonal back-up methods of contraception should be used during treatment with VOPREP and for 2 months following the last dose of VOPREP (see sections 4.4 and 4.5).

Pregnancy

For aprepitant no clinical data on exposed pregnancies are available. The potential for reproductive toxicity of aprepitant has not been fully characterised, since exposure levels above the therapeutic exposure in humans at the 125 mg/80 mg dose could not be attained in animal studies. Therefore, the safety and efficacy of PN in pregnancy has not been established as there are no adequate and well-controlled studies

Lactation

Aprepitant is excreted in the milk of lactating rats. It is not known whether aprepitant is excreted in human milk; therefore, breastfeeding is not recommended during treatment with [PRODUCT NAME].

Fertility

The potential for effects of aprepitant on fertility has not been fully characterised because exposure levels above the therapeutic exposure in humans could not be attained in animal studies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety pofile

Infections and infestations:

Less frequent: Candidiasis, staphylococcal infection.

Blood and lymphatic system disorders:

Less frequent: Febrile neutropenia, anaemia.

Immune system disorders:

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 flush/flushing.

Respiratory, thoracic and mediastinal disorders:

Frequent: Hiccups.

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

Gastrointestinal disorders:

Frequent: Constipation, dyspepsia.

Less frequent: Eructation, nausea, gastro-oesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence, hard faeces, duodenal ulcer perforation, stomatitis, abdominal distension, 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: Pruritus, urticaria.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle spasms, muscle weakness.

Renal and urinary disorders:

Less frequent: Dysuria, pollakiuria.

General disorders and administrative 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, glucose

present in urine, decreased neutrophil count.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of VOPREP is important. It allows continued monitoring of the benefit/risk balance of [PRODUCT NAME]. Healthcare 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.

4.9 Overdose

Symptoms

Drowsiness and headache were reported in one patient who ingested 1 440 mg of [PRODUCT NAME].

Treatment

No specific information is available on the treatment of overdosage with [PRODUCT NAME].

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

Because of the antiemetic activity of [PRODUCT NAME], emesis induced by another medicine may not be effective.

VOPREP 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

Aprepitant is a selective high-affinity antagonist at human substance P neurokinin 1 (NK_1) receptors. Aprepitant was at least 3 000-fold selective for the NK_1 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.

NK_1 receptor antagonist 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 NK_1 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-HT_3 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 %. The mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (t_{max}). Oral administration of the capsule with 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 aprepitant on Day 1 and 80 mg once daily on Days 2 and 3, the AUC_{0-24h} (mean ± SD) was approximately 19,5 µg•h/mL and

20,1 µg•h/mL on Days 1 and 3, respectively. The C_{max} of 1,5 µg/mL and 1,4 µg/mL was reached in approximately 4 hours (T_{max}) on Days 1 and 3, respectively.

Distribution:

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 in rats and crosses the blood brain barrier in rats and ferrets. PET studies in humans indicate that aprepitant crosses the blood-brain barrier (section 5.1).

Metabolism:

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 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, and no metabolism by CYP2D6, CYP2C9 or CYP2E1.

Elimination:

Aprepitant is eliminated primarily by metabolism, but is not renally excreted. Following a single oral 300 mg dose of [^{14}C]-aprepitant, 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 terminal half-life ranged from approximately 9 to 13 hours.

Special populations:

Gender

Following oral administration of a single 125 mg dose of aprepitant the $AUC_{0\text{-}24h}$ and C_{max} for aprepitant are 9 % and 17 % higher, respectively, in females as compared to 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 dose adjustment is necessary based on gender.

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 $AUC_{0\text{-}24h}$ of aprepitant was 21 % higher on Day 1 and 36 % higher on Day 5 in elderly (≥ 65 years) 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 dose adjustment for aprepitant is necessary in elderly patients.

Hepatic insufficiency

Aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125 mg dose 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 $AUC_{0\text{-}24h}$ of aprepitant was 11 % lower on Day 1 and 36 % lower on Day 3, as compared with healthy individuals given the same regimen.

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the $AUC_{0\text{-}24h}$ of aprepitant was 10 % higher on Day 1 and 18 % higher on Day 3, as compared with healthy individuals given the same regimen.

However, these differences in $AUC_{0\text{-}24h}$ are not considered clinically meaningful; therefore, no dosage adjustment for aprepitant 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 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 individuals. 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 dosage adjustment for aprepitant is necessary for patients with severe renal insufficiency or for patients with ESRD, undergoing haemodialysis.

Paediatric population

The pharmacokinetics of aprepitant have not been evaluated in patients below the age of 18 years.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Hypromellose

Microcrystalline cellulose

Poloxamer

Sucrose

Capsule shell (80 mg)

Gelatin

Sodium laurilsulfate

Titanium dioxide (E171)

Capsule shell (125 mg)

Gelatin

Iron oxide red (E172)

Sodium laurilsulfate

Titanium dioxide (E171)

Printing ink

Black iron oxide (E172)

Propylene glycol (E1520)

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

Store at or below 25 °C.

6.4 Special precautions for storage

Keep the blister strip in the outer carton until required for use.

Nature and contents of container

Aluminium/aluminium blister strips in an outer carton.

Pack sizes: 5 or 10 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

South Africa

8. REGISTRATION NUMBERS

VOPREP 80: 53/5.7.2/0448.445

VOPREP 125: 53/5.7.2/0449.446

VOPREP Combi Pack: 53/5.7.2/0450.447

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 June 2023

10. DATE OF REVISION OF THE TEXT