Applicant/PHCR: DR REDDY'S LABORATORIES (PTY) LTD
Product proprietary name: NAUSAP 150 IV
Dosage form: Lyophilised powder for solution for infusion
Strength: Each vial contains 245,3 mg of fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant free acid

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

NAUSAP 150 IV, 150 mg, Lyophilised Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NAUSAP 150 IV

Each vial contains 245,3 mg of fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant free acid as sterile, lyophilised powder.

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

Contains sugar (lactose anhydrous) 375 mg per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lyophilised powder for solution for infusion.

White to off-white lyophilised cake or powder

(lyophilised formulation for reconstitution and dilution prior to intravenous infusion).

NAUSAP 150 IV reconstituted solution: A clear, pale yellow coloured solution, free from visible extraneous matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NAUSAP 150 IV**,** 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

NAUSAP 150 IV for intravenous administration is a lyophilised pro-drug of aprepitant. NAUSAP 150 IV is administered on Day 1 as an infusion over 20 to 30 minutes initiated approximately 30 minutes prior to chemotherapy. NAUSAP 150 IV 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 NAUSAP 150 IV.

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

Highly Emetogenic Chemotherapy Regimen				
	Day 1	Day 2	Day 3	Day 4
NAUSAP 150 IV	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	None	None	None

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

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

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

Moderately Emetogenic Chemotherapy Regimen	
	Day 1
NAUSAP 150 IV	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 interactions.

General information

See section 4.5 for additional information on the administration of NAUSAP 150 IV with corticosteroids.

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

Special populations

Elderly (≥ 65 years)

No dosage adjustment is necessary for the elderly.

Gender

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) (see section 4.4).

Method of administration

NAUSAP 150 IV is administered by intravenous infusion over a 20 to 30-minute period. NAUSAP 150 IV should not be given by the intramuscular or subcutaneous route.

For instructions on reconstitution/dilution of the medicine before administration, see

section 6.6.

4.3 Contraindications

NAUSAP 150 IV is contraindicated in patients who are hypersensitive to aprepitant, polysorbate 80 or to any of the excipients listed in section 6.1.

NAUSAP 150 IV 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).

Pregnancy and lactation (see section 4.6).

Paediatric use

Safety and efficacy of NAUSAP 150 IV in paediatric patients have not been established.

4.4 Special warnings and precautions for use

Severe hepatic insufficiency

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 NAUSAP 150 IV is administered in these patients.

CYP3A4 interactions

Since NAUSAP 150 IV is rapidly converted to aprepitant (a weak to moderate inhibitor of CYP3A4), NAUSAP 150 IV should be used with caution in patients receiving concomitant medicines that are primarily metabolised through CYP3A4; some chemotherapy medicines are metabolised by CY3A4 (see section 4.5). Weak

inhibition of CYP3A4 by NAUSAP 150 IV could result in elevated plasma concentrations of these concomitant medicines (see section 4.5). Concomitant administration of NAUSAP 150 IV with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, telithromycin, 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 (see section 4.5).

Hypersensitivity

Immediate hypersensitivity reactions including flushing, erythema, dyspnoea, and anaphylaxis/anaphylactic shock have occurred during or soon after infusion of NAUSAP 150 IV. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. It is not recommended to re-initiate the infusion in patients who experience hypersensitivity reactions.

Warfarin

Co-administration of NAUSAP 150 IV with warfarin may result in a clinically significant decrease in the prothrombin time or International Normalised Ratio (INR). In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be closely monitored in the 2 week period, particularly at 7 to 10 days following initiation of NAUSAP 150 IV with each chemotherapy cycle (see section 4.5).

Hormonal contraceptives

The efficacy of hormonal contraceptives during and for 28 days after administration of NAUSAP 150 IV may be reduced. Alternative non-hormonal back-up methods of

contraception should be used during treatment with NAUSAP 150 IV and for 1 month following the last dose (see section 4.5).

Use in the elderly

In clinical studies, the efficacy and safety of aprepitant 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. (see section 4.2)

Administration and infusion site reactions

Infusion site reactions (ISRs) have been reported with the use of NAUSAP 150 IV (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.

NAUSAP 150 IV should not be given as a bolus injection, but should always be diluted and given as a slow intravenous infusion (see section 4.2). IVEMEND 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 medicines and other forms of interaction

When administered intravenously, fosaprepitant is rapidly converted to aprepitant. Therefore, interactions following administration of NAUSAP 150 IV, are likely to occur with medicines that interact with oral aprepitant.

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

Aprepitant is also an inducer of CYP2C9.

NAUSAP 150 IV, 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 NAUSAP 150 IV would cause less or no greater induction of CYP2C9 than that caused by the administration of oral aprepitant (see "Warfarin" and "Tolbutamide" below).

Aprepitant has been shown to induce the metabolism of S (-) warfarin and tolbutamide, which are metabolised through CYP2C9. Co-administration of NAUSAP 150 IV 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.

NAUSAP 150 IV is unlikely to interact with medicines that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of oral aprepitant with digoxin in a clinical interaction study.

The following information was derived from studies conducted with oral aprepitant and studies conducted with intravenous single-dose 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.

NAUSAP 150 IV 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 NAUSAP 150 IV and 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: NAUSAP 150 IV administered as a single intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, a CYP3A4 substrate, by approximately 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 NAUSAP 150 IV on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without NAUSAP 150 IV (see section 4.2).

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.

Chemotherapeutic medicines

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, NAUSAP 150 IV is not expected to have a clinically relevant interaction with intravenously administered docetaxel and vinorelbine.

Docetaxel: In a separate pharmacokinetic study, oral aprepitant, (CINV regimen) did not influence the pharmacokinetics of docetaxel.

Vinorelbine: In a separate pharmacokinetic study, oral aprepitant, (CINV regimen) did not influence the pharmacokinetics of vinorelbine.

An interaction with orally administered chemotherapeutic medicines metabolised primarily or partly by CYP3A4 (e.g. etoposide, vinorelbine) cannot be excluded. Caution and careful monitoring are advised in patients receiving etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan and paclitaxel or other chemotherapy agents 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

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. cyclosporine, 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 NAUSAP 150 IV.

Midazolam

NAUSAP 150 IV 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 Days 1 and 4. NAUSAP 150 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 NAUSAP 150 IV was administered as a dose of 100 mg 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 Day 1 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 NAUSAP 150 IV.

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 NAUSAP 150 IV 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 NAUSAP 150 IV.

Warfarin

A single 125 mg dose of oral aprepitant 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 oral aprepitant 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 oral aprepitant. 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 fosaprepitant with each chemotherapy cycle.

Prothrombin time (INR) should be done more frequently while using NAUSAP 150 IV.

Tolbutamide

Oral aprepitant, 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 oral aprepitant and on Days 4, 8 and 15.

Diabetic patients using tolbutamide should be monitored for glucose changes.

Oral contraceptives

Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg 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 oral aprepitant, 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 8 and 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 much as a 64 % decrease in ethinylestradiol trough concentrations during Days 9 through 21. While there was no effect on oral aprepitant 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 NAUSAP 150 IV may be reduced. Alternative non-hormonal back-up methods of contraception should be used during treatment with fosaprepitant or aprepitant and for 1 month following the last dose.

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 when given as regimen of 125 mg on Day 1 and 80 mg on Days 2 and 3, 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 150 mg and 5-HT_3 antagonists.

Effect of other medicines on the pharmacokinetics of aprepitant

NAUSAP 150 IV should be used with caution in patients receiving concomitant

medicines, including chemotherapy medicines that are primarily metabolised through CYP3A4.

Aprepitant is a substrate for CYP3A4; therefore, co-administration of NAUSAP 150 IV with medicines that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of NAUSAP 150 IV with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, troleandomycin, clarithromycin, telithromycin, 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 be approached with caution.

Aprepitant is a substrate for CYP3A4; therefore, co-administration of NAUSAP 150 IV with medicines that strongly induce CYP3A4 activity (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital) should be avoided as the combination may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of NAUSAP 150 IV.

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

Ketoconazole

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

Rifampicin

When a single 375 mg dose of oral aprepitant 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 approximately 11-fold and the mean terminal half-life decreased approximately 3-fold. Co-administration of fosaprepitant or aprepitant with medicines that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy.

Additional interactions

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 1,5-fold increase of aprepitant AUC and a 1,4-fold increase in diltiazem AUC. The pharmacokinetic effects resulted in a clinically meaningful decrease in diastolic blood pressure (decrease of 16,8 mm Hg with fosaprepitant versus 10,5 mm Hg without fosaprepitant) and may result in a clinically meaningful decrease in systolic blood pressure (decrease of 24,4 mm Hg with fosaprepitant versus 18,8 mm Hg without fosaprepitant), but did not result in a clinically meaningful change in heart rate, or PR interval beyond those changes induced by diltiazem alone.

In the same study, administration of aprepitant 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 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, 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 C_{max} by approximately 20 % of both aprepitant and paroxetine.

4.6 Fertility, pregnancy and lactation

NAUSAP 150 IV is contraindicated in pregnancy and lactation.

Contraception in males and females

The efficacy of hormonal contraceptives may be reduced during and for 28 days after administration of NAUSAP 150 IV.

Alternative non-hormonal back-up methods of contraception should be used during treatment with NAUSAP 150 IV and for 1 month following the last dose of NAUSAP 150 IV (see sections 4.4 and 4.5).

Pregnancy

Safety in pregnancy and lactation has not been established.

Breast-feeding

Mothers on treatment with NAUSAP 150 IV should not breastfeed their infants.

Aprepitant is excreted in the milk of lactating rats. It is not known whether aprepitant is excreted in human milk.

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

No studies of the effects of NAUSAP 150 IV on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with NAUSAP 150 IV may affect some patient's ability to drive or operate machinery. Dizziness and fatigue may occur following administration of NAUSAP 150 IV. Even though individual responses to NAUSAP 150 IV may vary, caution should be recommended when driving a car or operating machines (see section 4.8).

4.8 Undesirable effects

Since NAUSAP 150 IV is converted to aprepitant, those adverse experiences associated with aprepitant are also expected to occur with NAUSAP 150 IV.

Oral aprepitant:

Highly and Moderately Emetogenic Chemotherapy:

The following 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 or in postmarketing use.

Infections and infestations

Less frequent:

Candidiasis, staphylococcal infection

Blood and the lymphatic system disorders

Less frequent:

Anaemia, febrile neutropenia

Immune system disorders

Frequency not known:

Hypersensitivity reactions including anaphylactic reactions

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 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, gastroesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence, hard faeces, duodenal ulcer perforation, neutropenic colitis, stomatitis, abdominal distension

Skin and subcutaneous tissue disorders

Less frequent:

Rash, acne, photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, pruritic rash, Stevens-Johnson syndrome/toxic epidermal necrolysis

Frequency not known:

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 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

Fosaprepitant:

In an active-controlled clinical study in adult patients receiving highly emetogenic chemotherapy (HEC), safety was evaluated for 1 143 patients receiving the 1-day regimen of fosaprepitant 150 mg compared to 1 169 patients receiving the 3-day regimen of aprepitant.

Additionally, in a placebo-controlled clinical trial in adult patients receiving moderately emetogenic chemotherapy (MEC), safety was evaluated for 504 patients receiving a single dose of fosaprepitant 150 mg compared to 497 patients receiving the control regimen.

The safety profile was generally similar to that seen in the aprepitant studies as described above.

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

Infusion site reactions (ISRs) have been reported with the use of IVEMEND (see section 4.4)

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 pruritus, infusion site pain, infusion site induration

Frequency not known:

Immediate hypersensitivity reactions including flushing, erythema, dyspnoea, anaphylactic reactions/anaphylactic shock (see section 4.4).

Investigations

Less frequent:

Increased blood pressure

Other studies:

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

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

4.9 Overdose

In the event of overdose, NAUSAP 150 IV 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

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

Its anti-emetic effects are attributable to aprepitant.

NK_1-receptor antagonists inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Human Positron Emission Tomography

(PET) studies with aprepitant 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 apparent 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 blood brain barrier and placenta.

Metabolism

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 lung, kidney 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]-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 free acid) to aprepitant, 23,9 mg of phosphoric acid and 95,3 mg of meglumine are liberated.

Elimination

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

Special populations

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 (ESRD) 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; less than 0,2 % of the dose was recovered in the dialysate.

No dose 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

Edetate disodium anhydrous

Lactose anhydrous

Polysorbate 80

Sodium hydroxide (for pH adjustment) and/or

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

NAUSAP 150 IV is incompatible with any solutions containing divalent cations (e.g. Ca^{2+}, Mg^{2+}), including Hartman's and Lactated Ringer's Solution.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

The reconstituted final medicine solution is stable for 24 hours at ambient room temperature (at or below 25 °C). It must be used within 24 hours when stored at or below 25 °C.

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.

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

NAUSAP 150 IV powder for solution for infusion is filled in a clear 10 ml Type I glass vial sealed with a grey bromobutyl rubber stopper and an aluminium cap with a red

plastic flip-off seal, packed into cartons as single units.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

NAUSAP 150 IV must be reconstituted and then diluted prior to administration.

Preparation of NAUSAP 150 IV for intravenous administration

1. Inject 5 ml saline (0,9 % sodium chloride) into the vial. Assure that saline (0,9 % sodium chloride) is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting saline (0,9 % sodium chloride) into the vial. After reconstitution, use only if the solution is a clear, pale yellow coloured solution, free from visible particles.
2. Prepare an infusion bag filled with 145 ml of saline (0,9 % sodium chloride).
3. Withdraw the entire volume from the vial and transfer it into an infusion bag containing 145 ml of saline (0,9 % sodium chloride) to yield a total volume of 150 ml. Gently invert the bag 2 to 3 times.

NAUSAP 150 IV should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit.

For single use only.

Discard any remaining solution and waste material. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER

53/5.7.2/0458

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 November 2022

10 DATE OF REVISION OF TEXT

To be allocated.