Applicant : Eurolab (Pty) Ltd
Proprietary name : Aprepitant Eurolab, 80 mg & 125 mg & Combi pack
Dosage form and strength : Hard capsules, 80 mg & 125 mg
Date of submission : 12 May 2020
Approval date : 29 September 2020

APPROVED PROFESSIONAL INFORMATION FOR APREPITANT EUROLAB

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

APREPITANT 80 EUROLAB hard capsules

APREPITANT 125 EUROLAB hard capsules

APREPITANT COMBI PACK EUROLAB hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

APREPITANT 80 EUROLAB: Each hard capsule contains 80 mg of aprepitant.

APREPITANT 125 EUROLAB: Each hard capsule contains 125 mg of aprepitant.

CONTAINS SUGAR

Each 80 mg capsule contains 80 mg of sucrose

Each 125 mg capsule contains 125 mg of sucrose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

APREPITANT 80 EUROLAB: Opaque size 2 hard gelatin capsules with a white body and cap containing white to off white pellets.

APREPITANT 125 EUROLAB: Opaque size 1 hard gelatin capsules with a white body and pink cap containing white to off white pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

APREPITANT EUROLAB 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

Adults

APREPITANT EUROLAB is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose is 125 mg orally once daily one hour before start of chemotherapy on Day 1 and 80 mg orally once daily on Days 2 and 3 in the morning.

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

Highly Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3	Day 4
APREPITANT EUROLAB	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
5-HT_3 antagonists	Standard dose of 5-HT_3	None	None	None

	antagonists. See the product information for selected 5-HT_3 antagonists for appropriate dosing information.			

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

Moderately Emetogenic Chemotherapy Regimen

	Day 1	Day 2	Day 3
APREPITANT EUROLAB	125 mg orally	80 mg orally	80 mg orally
Dexamethasone	12 mg orally	None	None
5-HT_3 antagonists	Standard dose of 5-HT_3 antagonists. See the product information for selected 5-HT_3 antagonists for appropriate dosing	None	None

	information.		

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

The safety and efficacy of **APREPITANT EUROLAB** capsules have not been demonstrated in children. No data is available.

General

For additional information on the co-administration with corticosteroids, see section 4.5. Please refer to the SmPC of co-administered 5-HT_3 antagonist medicinal products.

Special populations

Elderly (≥ 65 years)

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

Gender

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

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

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). Aprepitant should be used with caution in these patients (see sections 4.4 and 5.2).

Method of administration

For oral use. The hard capsule should be swallowed whole.

APREPITANT EUROLAB may be taken with or without food.

4.3 Contraindications

- **APREPITANT EUROLAB** is contraindicated in patients with a known hypersensitivity to aprepitant or to any of the ingredients of **APREPITANT EUROLAB** (see section 6.1).
- **APREPITANT EUROLAB** should not be used concurrently with pimozide, 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 efficacy in paediatric patients have not been established.

4.4 Special warnings and precautions for use

Patients with moderate to severe hepatic impairment

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

CYP3A4 interactions

APREPITANT EUROLAB 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 cyclosporine, tacrolimus, sirolimus, and quinidine (see section 4.5). Additionally, concomitant administration with irinotecan should be approached with particular caution as the combination might result in increased toxicity.

Co-administration with warfarin (a CYP2C9 substrate)

In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely during treatment with **APREPITANT EUROLAB** and for 14 days following each 3-day course of **APREPITANT EUROLAB** (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 **APREPITANT EUROLAB**. Alternative non-hormonal back-up methods of contraception should be used during treatment with **APREPITANT EUROLAB** and for 1 month following the last dose of **APREPITANT EUROLAB** (see section 4.5).

Excipients

APREPITANT EUROLAB capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take **APREPITANT EUROLAB**.

APREPITANT EUROLAB capsules contain sodium. This medicinal product 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, as in **APREPITANT EUROLAB**, is a substrate, a moderate inhibitor and an inducer of CYP3A4. Aprepitant, as in **APREPITANT EUROLAB**, is also an inducer of CYP2C9. During treatment with Aprepitant, as in **APREPITANT EUROLAB**, CYP3A4 is inhibited. After the end of treatment, Aprepitant, as in **APREPITANT EUROLAB**, causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation. Aprepitant, as in **APREPITANT EUROLAB**, does not seem to interact with the P-glycoprotein transporter, as suggested by the lack of interaction of Aprepitant, as in **APREPITANT EUROLAB**, with digoxin.

Effect of Aprepitant, as in **APREPITANT EUROLAB**, on the pharmacokinetics of other active substances

CYP3A4 inhibition

As a moderate inhibitor of CYP3A4, Aprepitant, as in **APREPITANT EUROLAB**, (125 mg/80 mg) can increase plasma concentrations of co-administered active substances that are metabolised through CYP3A4. The total exposure of orally administered CYP3A4 substrates may increase up to approximately 3-fold during the 3-day of treatment with Aprepitant, as in **APREPITANT EUROLAB**; the effect of Aprepitant, as in **APREPITANT EUROLAB**, on the plasma concentrations intravenously administered CYP3A4 substrates is expected to be smaller.

Aprepitant, as in **APREPITANT EUROLAB**, must not be used concurrently with pimozide, terfenadine, astemizole, or cisapride (see section 4.3). Inhibition of CYP3A4 by Aprepitant, as in **APREPITANT EUROLAB**, could result in elevated plasma concentrations of these active substances, potentially causing serious or life-threatening reactions. Caution is advised during concomitant administration of Aprepitant, as in **APREPITANT EUROLAB**, 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: The usual oral dexamethasone dose should be reduced by approximately 50 % when co-administered with Aprepitant, as in **APREPITANT EUROLAB**, regimen. The dose of dexamethasone in chemotherapy-induced nausea and vomiting clinical trials was chosen to account for active substance interactions (see section 4.2). Aprepitant, as in **APREPITANT EUROLAB**, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Days 1, and Aprepitant, as in **APREPITANT EUROLAB**, when given as 80 mg/day with dexamethasone co-administered orally as 8 mg on Days 2 and 5, increased the AUC of dexamethasone, a CYP3A4 substrate, 2,2-fold on Days 1 and 5.

Methylprednisolone: The usual intravenously administered methylprednisolone dose should be reduced approximately 25 %, and the usual oral methylprednisolone dose should be reduced approximately 50 % when co-administered with Aprepitant, as in **APREPITANT EUROLAB**, 125 mg/ 80 mg regimen. Aprepitant, as in **APREPITANT EUROLAB**, 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.

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 EUROLAB**, dose, due to the inducing effect of Aprepitant, as in **APREPITANT EUROLAB**, on CYP3A4. This effect may be expected to be more pronounced for orally administered methylprednisolone.

Chemotherapeutic medicinal products

In pharmacokinetics, Aprepitant, as in **APREPITANT EUROLAB**, when given as a regimen of 125 mg on Day 1 and 80 mg/ day on Days 2 and 3, did not influence the pharmacokinetics of docetaxel administered intravenously on Day 1 or vinorelbine administered intravenously on Day 1 or Day 8. Because the effect of Aprepitant, as in **APREPITANT EUROLAB**, on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of Aprepitant, as in **APREPITANT EUROLAB**, on the pharmacokinetics of intravenously administered CYP3A4 substrates, an interaction with orally administered chemotherapeutic medicinal products metabolised primarily or partly by CYP3A4 (e.g. etoposide, vinorelbine) cannot be excluded. Caution is advised and additional monitoring may be appropriate in patients receiving medicinal products 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, as in **APREPITANT EUROLAB**, and ifosfamide co-administration.

Immunosuppressants

During the 3-day CINV (Chemotherapy-Induced Nausea and Vomiting) 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 Aprepitant, as in **APREPITANT EUROLAB**.

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 medicinal products with Aprepitant, as in **APREPITANT EUROLAB** (125 mg /80 mg).

Aprepitant, as in **APREPITANT EUROLAB**, 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, as in **APREPITANT EUROLAB**, 125 mg on Day 1 and 80 mg /day on Days 2 to 5. In another study with intravenous administration of midazolam, Aprepitant, as in **APREPITANT EUROLAB**, 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, as in **APREPITANT EUROLAB**, and on Days 4, 8, and 15. Aprepitant, as in **APREPITANT EUROLAB**, 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, as in **APREPITANT EUROLAB**, 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, 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, as in **APREPITANT EUROLAB**. Intravenous 2 mg midazolam was given 1 hour after oral administration of a single dose of Aprepitant, as in **APREPITANT EUROLAB** 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, as in **APREPITANT EUROLAB**, can decrease plasma concentrations of substrates eliminated by these routes within two weeks following initiation of treatment. This effect may become apparent only after the end of a 3-day treatment with Aprepitant, as in **APREPITANT EUROLAB**. For CYP2C9 and CYP3A4 substrates the induction is transient with a maximum effect reached after 3-5 days after the end of the Aprepitant, as in **APREPITANT EUROLAB**, 3-day treatment. The effect is maintained for a few days, thereafter, slowly declines and is clinically insignificant by two weeks after the end of Aprepitant, as in **APREPITANT EUROLAB**, treatment. Mild induction of glucuronidation is also seen with 80 mg oral Aprepitant, as in **APREPITANT EUROLAB**, 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 time period.

Warfarin

In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with Aprepitant, as in **APREPITANT EUROLAB**, and for 2 weeks following each 3-day course of Aprepitant, as in **APREPITANT EUROLAB**, for chemotherapy-induced nausea and vomiting (see section 4.4). When a single 125 mg dose of Aprepitant, as in **APREPITANT EUROLAB**, was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilised on chronic warfarin therapy, there was no effect of Aprepitant, as in **APREPITANT EUROLAB**, on the plasma AUC of R(+) or S(-) warfarin determined on Day 3; however, 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 Aprepitant, as in **APREPITANT EUROLAB**.

Tolbutamide

Aprepitant, as in **APREPITANT EUROLAB**, 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, as in **APREPITANT EUROLAB**, 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 Aprepitant, as in **APREPITANT EUROLAB**. Alternative non-hormonal back-up methods of contraception should be used during treatment with Aprepitant, as in **APREPITANT EUROLAB**, and for 1 month following the last dose of Aprepitant, as in **APREPITANT EUROLAB**.

In a clinical study, a single dose of an oral contraceptive containing ethinyl estradiol and norethindrone were administered on Days 1 through 21 with Aprepitant, as in **APREPITANT EUROLAB**, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg intravenously on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. During days 9 through 21 in this study, there was as much as a 64 % decrease in ethinyl estradiol trough concentrations and as much as a 60 % decrease in norethindrone trough concentrations.

5-HT_3 antagonists

In clinical interaction studies, Aprepitant, as in **APREPITANT EUROLAB**, did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the

active metabolite of dolasetron).

Effect of other medicinal products on the pharmacokinetics of Aprepitant

Concomitant administration of Aprepitant, as in **APREPITANT EUROLAB**, with active substances that inhibit CYP3A4 activity (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and protease inhibitors) should be approached cautiously, as the combination is expected to result in several-fold increased plasma concentrations of Aprepitant, as in **APREPITANT EUROLAB**, (see section 4.4). Concomitant administration of Aprepitant, as in **APREPITANT EUROLAB**, 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, as in **APREPITANT EUROLAB**, that may result in decreased efficacy of Aprepitant, as in **APREPITANT EUROLAB**. Concomitant administration of Aprepitant, as in **APREPITANT EUROLAB**, with herbal preparations containing St. John's Wort (Hypericum perforatum) is not recommended.

Ketoconazole

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

Rifampicin

When a single 375 mg dose of Aprepitant, as in **APREPITANT EUROLAB**, was administered on Day 9 of a 14-day regimen of 600 mg /day of rifampicin, a strong CYP3A4 inducer, the AUC

of Aprepitant, as in **APREPITANT EUROLAB**, decreased 91 % and the mean terminal half-life decreased 68 %.

Paroxetine

Co-administration of once daily doses of Aprepitant, as in **APREPITANT EUROLAB**, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25 % and C_{max} by approximately 20 % of both Aprepitant, as in **APREPITANT EUROLAB**, and paroxetine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

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

Pregnancy

Safety in pregnancy has not been established, since there are no adequate and well-controlled studies in pregnant woman.

Breastfeeding

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

APREPITANT EUROLAB.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The frequency categories given in the table are based on adults.

The following headings are used to rank the ADRs by frequency: frequent, less frequent,

frequency unknown

Body System	Frequent	Less Frequent	Frequency Unknown
Infections and infestations		Candidiasis, staphylococcal infection	
Blood and lymphatic system disorders		Febrile neutropenia, anaemia	
Immune system disorders			Hypersensitivity reactions including anaphylactic reactions
Metabolism and nutrition disorders	Decreased appetite	Polydipsia	
Psychiatric disorders		Anxiety, Disorientation, euphoric mood	
Nervous system disorders	Headache	Dizziness, somnolence, Cognitive disorder, lethargy, dysgeusia	
Eye disorders		Conjunctivitis	
Ear and labyrinth disorders		Tinnitus	

Body System	Frequent	Less Frequent	Frequency Unknown
Cardiac disorders		Palpitations, Bradycardia, cardiovascular disorder	
Vascular disorders		Hot flushes /flushing	
Respiratory, thoracic and mediastinal disorders	Hiccups	Oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation	
Gastrointestinal disorders	Constipation, dyspepsia	Eructation, nausea†, vomiting†, gastroesophageal reflux disease, abdominal pain, dry mouth, flatulence, duodenal ulcer perforation, stomatitis, abdominal distention, faeces hard, neutropenic colitis,	
Skin and subcutaneous tissue disorders		Rash, acne, photosensitivity reaction, hyperhidrosis,	Pruritus, urticarial

Body System	Frequent	Less Frequent	Frequency Unknown
		seborrhoea, skin lesion, rash prutitic, Stevens-Johnson syndrome/toxic epidermal necrolysis	
Muskuloskeletal and connective tissue disorders		Muscular weakness, muscle spasms	
Renal and urinary disorders		Dysuria, pollakiuria	
General disorders and administration site conditions	Fatigue	Asthenia, malaise, oedema, chest discomfort, gait disturbance	
Investigations	ALT increase	AST increase, blood alkaline phosphatase increased, red blood cells urine positive, blood sodium decreased, weight decreased, neutrophil count decreased, glucose urine present, urine	

Body System	Frequent	Less Frequent	Frequency Unknown
		output increased	

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

Description of selected adverse reactions

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

*Reported in patients taking a higher dose of **APREPITANT EUROLAB**.

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

Healthcare providers should also report adverse reactions to the Holder of Certificate of Registration (HCR), Eurolab (Pty) Ltd; **Contact details of the HCR:**

Email: info@eurolab.co.za

Tel. no.: +27 (0)11 656 0031

24-Hour Tel no.: 082 389 9048

4.9 Overdose

In the event of overdose, **APREPITANT EUROLAB** should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of **APREPITANT EUROLAB**, emesis induced by a medicinal product may not be effective. **APREPITANT EUROLAB** cannot be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: 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 (NK1) receptors. it is shown that aprepitant was at least 3000-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.

NK_1-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 penetrates the brain and occupies brain NK1 receptors. Aprepitant has long central activity duration, inhibits both the acute and delayed phases of cisplatin-induced emesis, and augments the anti-emetic activity of the $5\text{-}HT_3$-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

5.2 Pharmacokinetic properties

Absorption

The mean absolute oral availability 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 aprepitant capsules 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 aprepitant on day 1 and 80 mg once daily on day 2 and day 3, the $AUC_{0-\infty}$ was approximately 19,5 µg/hr/ml and 20,1 µg/hr/ml on day 1 and day 3 respectively. The C_{max} of 1,5 µg/ml and 1,4 µg/ml were reached in approximately 4 hours (T_{max}) on day 1 and day 3 respectively.

Distribution

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

Aprepitant crosses the placenta in rats and crosses the blood brain barrier in rats and ferrets. PET in humans indicate that aprepitant crosses the blood brain barrier (see section 5.1).

Metabolism

Aprepitant undergoes extensive metabolism. 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 and is not renally excreted. Following oral administration of a single oral 300 mg dose of [$_{14}$C]-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.

Special populations:

Elderly

The differences in AUC0-24hr and Cmax between younger adults and the elderly are not considered clinically meaningful. No dose adjustment is necessary based on age.

Paediatric

No pharmacokinetic data is available for patients under 18 years of age.

Hepatic impairment

Aprepitant is well tolerated in patients with mild to moderate hepatic impairment. The difference in AUC0-24hr between patients with mild to moderate hepatic impairment (Child-Pugh score of 5-6 and 7-9 respectively) and healthy subjects are not considered clinically meaningful. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment.

There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).

Renal impairment

The difference in AUCt-∞ and Cmax between patients with severe renal insufficiency (CrCl < 30 ml/min) and patients with end stage renal disease (ESRD) on haemodialysis, and healthy subjects, are not considered clinically-meaningful. No dosage adjustment is necessary for patients with severe renal impairment or for patients with ESRD undergoing haemodialysis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Sucrose

Cellulose, Microcrystalline Sphere 500 (E460)

Hydroxypropylcellulose (E463) (HPC-SL)

Sodium Laurilsulfate

Capsule Body:

Gelatin

Titanium Dioxide (E171)

Capsule Cap:

Gelatin

Titanium Dioxide (E171)

Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

APREPITANT 80 EUROLAB and **APREPITANT 125 EUROLAB** hard capsules are packed in a carton containing 5 capsules individually packaged in single Alu-OPA/Alu/PVC foil blisters. Each carton contains 5 blisters.

APREPITANT COMBIPACK EUROLAB are packaged in a carton containing individually packaged in single Alu-OPA/Alu/PVC foil blister packs as a combination one 125 mg capsule and two 80 mg capsules in a carton.

6.6 Special precautions for disposal

Procedures for safe handling of cytotoxic medicines should be followed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue

Woodmead

2144

8 REGISTRATION NUMBER(S)

APREPITANT 80 EUROLAB: A53/5.7.2/0234

Namibia Reg No.: NS2 21/5.7.2/0034

Tanzania Reg No.: TAN 21 HM 0337

APREPITANT 125 EUROLAB: A53/5.7.2/0235

Namibia Reg No.: NS2 21/5.7.2/0035

Tanzania Reg No.: TAN 21 HM 0336

APREPITANT COMBI PACK EUROLAB: A53/5.7.2/0236

Namibia Reg No.: NS2 21/5.7.2/0036

Tanzania Reg No.: TAN 21 HM 0335

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2020