Approved Professional Information for Medicines for Human Use:

GOMESIS 80 mg/ 125 mg/ Combi pack

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GOMESIS 80 mg Capsules

GOMESIS 125 mg Capsules

GOMESIS COMBI PACK (125 mg and 80 mg) Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GOMESIS 80 mg capsules

Each capsule contains 80 mg Aprepitant.

GOMESIS 125 mg capsules

Each capsule contains 125 mg Aprepitant.

Contains sugar (sucrose)

GOMESIS 80 mg capsules

Each capsule contains 80 mg sucrose.

GOMESIS 125 mg capsules

Each capsule contains 125 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsule.

GOMESIS 80 mg capsules

Opaque, size 2 hard gelatin capsules with a white body and cap, containing white to off-white pellets.

GOMESIS 125 mg capsules

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

GOMESIS 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

GOMESIS 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 (PI) for the co-administered 5-HT_3 antagonist must be consulted prior to initiation of treatment with GOMESIS. The recommended dose of GOMESIS is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.

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

	Day 1	Day 2	Day 3	Day 4
GOMESIS	125 mg	80 mg	80 mg	None
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
5-HT_3 antagonist	See the professional information for the selected 5-HT_3 antagonist for appropriate dosing information	None	None	None

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

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

	Day 1	Day 2	Day 3
-GOMESIS	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 section 4.5 for additional information on the administration of GOMESIS with corticosteroids.

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

Special populations

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

Elderly

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

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) (see sections 4.4 and 5.2).

Paediatric population

Safety and effectiveness in paediatric patients have not been established.

Method of administration

GOMESIS is for oral administration.

The hard capsule should be swallowed whole.

GOMESIS may be taken with or without food.

4.3 Contraindications

GOMESIS is contraindicated in patients who are hypersensitive to aprepitant or to any of the excipients listed in section 6.1

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

Safety and effectiveness 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. GOMESIS should be used with caution in these patients (see section 5.2).

CYP3A4 inhibition

GOMESIS should be used with caution in patients receiving concomitant medicines that are metabolised primarily through CYP3A4; Some chemotherapeutic medicines are metabolised by CYP3A4 (see section 4.5). Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicines (see section 4.5). Consequently, concomitant administration of GOMESIS with strong CYP3A4 inhibitors (e.g. ketoconazole,

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

Co-administration with warfarin (a CYP2C9 substrate)

Co-administration of GOMESIS with warfarin may result in a clinically significant decrease in International Normalised Ratio (INR) or prothrombin time. In patients on chronic warfarin therapy, the International Normalised Ratio (INR) should be monitored closely during treatment with GOMESIS and for 14 days following each 3-day course of GOMESIS (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 GOMESIS. Alternative nonhormonal back-up methods of contraception should be used during treatment with GOMESIS and for 2 months following the last dose of GOMESIS (see section 4.5).

Sucrose intolerance

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

Sodium

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

4.5 Interaction with other medicines and other forms of interaction

Aprepitant (125 mg/ 80 mg) is a substrate, a moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with GOMESIS, CYP3A4 is inhibited. After the end of treatment, GOMESIS causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation. Aprepitant does not seem to interact with the P-glycoprotein transporter, as suggested by the lack of interaction of aprepitant with digoxin.

Effect aprepitant on the pharmacokinetics of other active substances

CYP3A4 inhibition

As a moderate inhibitor of CYP3A4, aprepitant (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 treatment with aprepitant capsules; the effect of aprepitant on the plasma concentrations of intravenously administered CYP3A4 substrates is expected to be smaller. GOMESIS 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 GOMESIS 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 GOMESIS 125 mg/80 mg regimen. The dose of dexamethasone in chemotherapy induced nausea and vomiting (CINV) clinical trials was chosen to account for active substance interactions (see section 4.2). Aprepitant capsules, when given as a regimen of 125 mg with dexamethasone co-administered orally as 20 mg on Day 1, and aprepitant capsules 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.

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 GOMESIS 125 mg/80 mg regimen. Aprepitant capsules, 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 capsules dose, due to the inducing effect of aprepitant on CYP3A4. This effect may be expected to be more pronounced for orally administered methylprednisolone.

Chemotherapeutic medicines

In pharmacokinetic studies, aprepitant capsules, 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 capsules on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of aprepitant capsules on the pharmacokinetics of intravenously administered CYP3A4 substrates, an interaction with orally administered chemotherapeutic medicines 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 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 GOMESIS.

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 GOMESIS (125 mg/80 mg).

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

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

In a third study with intravenous and oral administration of midazolam, aprepitant capsules was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, together with ondansetron 32 mg Day 1, dexamethasone 12 mg Day 1 and 8 mg Days 2-4. This combination (i.e. aprepitant capsules, ondansetron and dexamethasone)

decreased the AUC of oral midazolam 16 % on Day 6, 9 % on Day 8, 7 % on Day 15 and 17 % on Day 22. These effects were not considered clinically important.

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

Induction

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

Warfarin

In patients on chronic warfarin therapy, the prothrombin time (INR) should be monitored closely during treatment with GOMESIS and for 2 weeks following each 3-day course of GOMESIS for chemotherapy induced nausea and vomiting (see

section 4.4). When a single 125 mg dose of aprepitant capsules 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 capsules 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 capsules.

Tolbutamide

Aprepitant capsules, 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 GOMESIS 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 GOMESIS. Alternative nonhormonal back-up methods of contraception should be used during treatment with GOMESIS and for 2 months following the last dose of GOMESIS.

In a clinical study, single doses of an oral contraceptive containing ethinylestradiol and norethindrone were administered on Days 1 through 21 with aprepitant capsules, 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 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 aprepitant capsules, such as GOMESIS 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 several-fold in increased plasma concentrations of aprepitant (see section 4.4).

Concomitant administration of aprepitant capsules, such as GOMESIS with active substances that strongly induce CYP3A4 activity (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital) should be avoided as the combination results in reductions of the plasma concentrations of aprepitant that may result in decreased efficacy of GOMESIS. Concomitant administration of GOMESIS with herbal preparations containing St. John's Wort (*Hypericum perforatum)* is not recommended.

Ketoconazole

When a single 125 mg dose of 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.

Rifampicin

When a single 375 mg dose of 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 91 % and the mean terminal half-life decreased 68 %.

Other interactions

Diltiazem

In patients with mild to moderate hypertension, administration of GOMESIS 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 GOMESIS 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 GOMESIS, 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 GOMESIS and paroxetine.

Paediatric population

Interaction studies have only been performed in adults.

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 aprepitant capsules, such as GOMESIS. Alternative nonhormonal back-up methods of contraception should be used during treatment with GOMESIS and for 2 months following the last dose of GOMESIS (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. These studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. The potential effects on reproduction of alterations in neurokinin regulation are unknown. GOMESIS should not be used during pregnancy unless clearly necessary.

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 GOMESIS.

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. 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

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

4.8 Undesirable effects

Summary of the safety profile

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

Highly Emetogenic Chemotherapy (HEC)

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

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

Moderately Emetogenic Chemotherapy (MEC)

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

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

The most frequent aprepitant-related adverse experience reported at a greater incidence with the aprepitant regimen than with standard therapy was fatigue (14 %).

Tabulated list of adverse reactions

The following adverse reactions were observed in a pooled analysis of the HEC and MEC studies at a greater incidence with aprepitant than with standard therapy or in post-marketing use.

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with aprepitant.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
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	
Cardiac disorders		palpitations, bradycardia, cardiovascular disorder	
Vascular disorders		hot flush/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 distension, hard faeces, neutropenic colitis	
Skin and subcutaneous tissue disorders		rash, acne, photosensitivity reaction, hyperhidrosis,	pruritus, urticaria

		seborrhoea, skin lesion, rash pruritic, Stevens-Johnson syndrome/ toxic epidermal necrolysis	
Musculoskeletal 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	increased alanine aminotransferase (ALT)	increased aspartate transaminase (AST), increased blood alkaline phosphatase, positive red blood cells in urine,	

		decreased blood sodium, decreased weight, decreased neutrophil count, glucose present in urine, increased urine output	

†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

The adverse reactions profiles of aprepitant capsules in adults in the Multiple-Cycle extension of HEC and MEC studies for up to 6 additional cycles of chemotherapy were generally similar to those observed in Cycle 1.

In other reported clinical studies cases of serious adverse experiences were reported. Stevens-Johnson syndrome was reported in a patient receiving aprepitant with cancer chemotherapy in another CINV study. Angioedema and urticaria were reported in a

patient receiving aprepitant in a non-CINV study.

In an additional reported active-controlled clinical study with aprepitant capsules in 1 169 adult patients receiving aprepitant and HEC, the adverse reactions profile was generally similar to that seen in the other HEC studies with 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Drowsiness and headache were reported in one patient who ingested 1 440 mg of aprepitant.

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

Because of the antiemetic activity of aprepitant, emesis induced by a medicine may not be effective.

Aprepitant 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: Anti-emetics and antinauseants

ATC Code: A04AD12.

Aprepitant is a substance P neurokinin 1 (NK_1) receptor antagonist.

Aprepitant is a selective high affinity antagonist at human substance P neurokinin 1 (NK_1) receptors. Counter-screening assays showed that 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 antagonists have been shown pre-clinically to inhibit emesis induced by cytotoxic chemotherapeutic medicines, such as cisplatin, via central actions. Pre-clinical and human Positron Emission Tomography (PET) studies with aprepitant have shown that it is brain penetrant and occupies brain 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 % and the mean peak plasma concentration (C_{max}) of aprepitant occurred at approximately 4 hours (T_{max}). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

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

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

Distribution

Aprepitant is > 95 % bound to plasma proteins. The geometric mean apparent volume of distribution at steady state (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 (see section 5.1).

Biotransformation

Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 24 % of the radioactivity in plasma over 72 hours following a single oral 300 mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolised primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9 or CYP2E1.

Elimination

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. Following administration of a single oral 300 mg dose of [^{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.

Gender

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

Elderly

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

Hepatic insufficiency

Aprepitant capsules was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125 mg dose of aprepitant capsules 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 $AUC_{0\text{-}24hr}$ of aprepitant was 11 % lower on Day 1 and 36 % lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the $AUC_{0\text{-}24hr}$ of aprepitant was 10 % higher on Day 1 and 18 % higher on Day 3, as compared with healthy subjects given the same regimen. These differences in $AUC_{0\text{-}24hr}$ are not considered clinically meaningful; therefore, no dosage adjustment for GOMESIS 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 capsules 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 $AUC_{0\text{-}\infty}$ 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 $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42 % and C_{max} decreased by 32 %. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound medicine was not significantly affected in

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

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

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Hydroxypropylcellulose (E463)

Microcrystalline cellulose sphere 500 (E460)

Sodium laurilsulfate

Sucrose

Capsule shell (80 mg):

Gelatin

Titanium dioxide (E171)

Capsule shell (125 mg):

Gelatin

Iron oxide red (E172)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 30 ^{o}C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

GOMESIS 80 mg capsules are supplied in an outer carton containing one of the following:

- Aluminium-OPA/Alu/PVC blister containing one 80 mg capsule.
- Aluminium-OPA/Alu/PVC blister containing two 80 mg capsules.
- 5 Aluminium-OPA/Alu/PVC blisters each containing one 80 mg capsule.
- 3 Aluminium-OPA/Alu/PVC blisters each containing one 80 mg capsule.

GOMESIS 125 mg capsules are supplied in an outer carton containing one of the following:

- Aluminium-OPA/Alu/PVC blister containing one 125 mg capsule.
- 5 Aluminium- OPA/Alu/PVC blisters each containing one 125 mg capsule.

GOMESIS combi pack capsules are supplied in an outer carton containing the following:

- Aluminium-OPA/Alu/PVC blister containing one 125 mg capsule and two 80 mg capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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2193

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8. REGISTRATION NUMBERS

GOMESIS 80 mg capsules: 53/5.7.2/0084

GOMESIS 125 mg capsules: 53/5.7.2/0085

GOMESIS combi pack capsules: 53/5.7.2/0086.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022.

10. DATE OF REVISION OF THE TEXT

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