SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epzit 10 mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Domperidone

Each orodispersible tablet contains 10 mg Domperidone (as maleate)

Excipients: 7.5 mg of aspartame (E951)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

white to off-white, round, flat, beveled edged tablets, plain on both sides, having peppermint odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epzit 10 mg Orodispersible Tablets are indicated for the relief of the symptoms of nausea and vomiting.

4.2 Posology and method of administration

Epzit should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.

It is recommended to take Epzit 10 mg Orodispersible Tablets before meals. If taken after meals, absorption of the drug is somewhat delayed.

Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

Usually, the maximum treatment duration should not exceed one week.

See section 4.4. for further information.

Adults and adolescents (12 years of age and older and weighing 35 kg or more)

One 10mg tablet up to three times per day with a maximum dose of 30 mg per day.

Hepatic Impairment

Epzit 10 mg Orodispersible Tablets are contraindicated in moderate (Child-Pugh 7 to 9) or severe (Child-Pugh > 9) hepatic impairment (see section 4.3). Dose modification in mild (Child-Pugh 5 to 6) hepatic impairment is however not needed (see section 5.2).

Renal Impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6mg/100mL, i.e. 0.6 mmol/L), the dosing frequency of Epzit 10 mg Orodispersible Tablets should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients with severe renal impairment should be reviewed regularly (see section 4.4 and 5.2).

Paediatric population

The efficacy of Epzit in children less than 12 years of age has not been established (see section 5.1).

The efficacy of Epzit in adolescents 12 years of age and older and weighing less than 35 kg has not been established.

Method of administration

For oral use

The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference.

4.3 Contraindications

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Confirmed or suspected pheochromocytoma due to the risk of severe hypertension episodes
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g in patients with gastro- intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see section 5.2)
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see section 4.4)
- Co-administration with QT-prolonging drugs, at the exception of apomorphine (see sections 4.4 and 4.5)
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section 4.5)

4.4 Special warnings and precautions for use

Cardiovascular effects:

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section 4.8).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section 4.3.). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine

Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the apomorphine SmPC are strictly fulfilled. Please refer to the apomorphine SmPC.

Renal Impairment

The elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6mg/100mL, i.e. 0.6 mmol/L). The dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

Excipients

Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Co-administration of levodopa

Although no dosage adjustment of levodopa is deemed necessary, an increase of plasma levodopa concentration (max 30-40%) has been observed when domperidone was taken concomitantly with levodopa. See section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

The main metabolic pathway of domperidone is through CYP3A4. In vitro and human data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated

QTc prolonging medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) (see section 4.3).
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled. Please refer to the apomorphine SmPC.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e:

- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin telithromycin) (see section 4.3).

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides. (see section 4.3)

Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

Separate *in vivo pharmacokinetic/pharmacodynamic* interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the Cmax and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

Levodopa: Increase of plasma levels of levodopa (max 30-40%). See section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses (see section 5.3). Epzit should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

4.7 Effects on ability to drive and use machines

Somnolence have been observed following use of domperidone (see section 4.8). Therefore, patients should be advised not to drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how Domperidone affects them.

4.8 Undesirable effects

Tabulated list of adverse reactions

The safety of domperidone was evaluated in clinical trials and in postmarketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of Epzit (domperidone base). The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

The following terms and frequencies are applied:

very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Where frequency can not be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	Adverse Drug Reaction Frequency		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety Agitation Nervousness	
Nervous system disorders		Somnolence Headache Extrapyramidal disorder	Convulsion Restless leg syndrome*

Eye disorders			Oculogyric crisis
Cardiac disorders (see section 4.4)			Ventricular arrhythmias QTc prolongation Torsade de Pointes Sudden cardiac death
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus Urticaria	Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain Breast tenderness	Gynaecomastia Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

*exacerbation of restless legs syndrome in patients with Parkinson's disease

In 45 studies where domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store."

4.9 Overdose

Symptoms

Symptoms of over dosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Mechanism of action

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day). The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

Clinical Studies in infants and children 12 years of age and younger

A multicentre, double blinded, randomized, placebo controlled, parallel group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomized subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing vomiting episodes during the first 48 hours after the first treatment administration (see section 4.2).

5.2 Pharmacokinetic properties

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hour after dosing. The Cmax and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone’s bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take

domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drugis taken after a meal.

Distribution

Oral Domperidone does not appear to accumulate or to induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax of domperidone is 2.9- and 1.5- fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25 %, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on Cmax and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance <30 ml/min/1.73m^2) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy

volunteers. Since very little unchanged drug (approximately 1%) is excreted *via* the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency.

However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric population

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In *in-vitro* experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26 - 47-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10mg administered 3 times a day. Safety margins for prolongation of action potential duration in *in-vitro* experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by 45 fold. Safety margins in *in-vitro* proarrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by 9- up to 45-fold.In *in-vivo* models the no-effect levels for QTc prolongation in dogs and induction of arrhythmias in rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-fold.

At a high, maternally toxic dose (more than 40 times the recommended oral human dose based on body surface area dose comparisons (mg/m^2)), teratogenic effects (organ abnormalities such as anophthalmia, microphthalmia and displacement of the subclavian artery) were seen in the rat. At a higher dose (more than 14 times the maximum recommended oral human dose), no teratogenic effects were observed. The clinical relevance of these animal findings is unknown. No teratogenicity was observed in mice and rabbits.

Electrophysiological in vitro and in vivo studies have shown that domperidone, at high concentrations, may prolong the QTc interval

No adverse effects were observed in juvenile rats at clinically relevant doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Silica, Colloidal Anhydrous

Cellulose, Microcrystalline

Aspartame (E951)

Crospovidone

Peppermint flavour

Magnesium Stearate

6.2 Incompatibilities

None applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original pack in order to protect from moisture.

6.5 Nature and contents of container

Blister packs comprising Alu-Alu (OPA/Alu/PVC-Alu)

Pack sizes: 10, 20, 30, 50 or 100 Orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novumgen Limited
20-22 Wenlock Road, London,
N1 7GU, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 55863/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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