

**For the use of a Registered Medical Practitioner or Hospital or a Laboratory only**

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## **DOMSTAL RD**

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### **1. GENERIC NAME**

Omeprazole and Domperidone Capsules I.P.

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard gelatin capsule contains:

Omeprazole I.P. ....20mg

(as enteric coated pellets)

Domperidone Maleate I.P. equivalent to

Domperidone ..... 10 mg

(as pellets)

Colours: Yellow Oxide of Iron

Red Oxide of Iron and Titanium Dioxide I.P.

Approved colours used in hard gelatin capsule shell

OTHER INACTIVE INGREDIENTS are HYDROXY PROPYL METHYL CELU., MAGNESIUM STEARATE, FERRIC OXIDE YELLOW, FERRIC OXIDE RED, TALC, ETHYL CELLULOSE, METHANOL, METHYLENE CHLORIDE, SUGAR GLOBULE, TITANIUM DIOXIDE, Met. Acid&Eth. Acr.co., PEG -6000.

### **3. DOSAGE FORM and Strength**

Hard gelatin capsule

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

For the treatment of Gastroesophageal Reflux Disease (GERD) not responding to Omeprazole alone

#### **4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

One capsule twice daily or as directed, do not take more than allowed maximum individual component dose. Maximum allowed dose for omeprazole is 40mg and for domperidone is 80mg.

#### **4.3 CONTRAINDICATIONS**

Contraindicated in the following situations:

- Known hypersensitivity to omeprazole, domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- when stimulation of the gastric motility could be harmful e.g in patients with gastrointestinal
- haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment.
- 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.
- Co-administration with QT-prolonging drugs.
- co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging Effects).
- Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly With nelfinavir.

#### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

##### **Omeprazole**

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients. Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

### Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

### Interference with laboratory tests

Increased Chromogranin a (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Omeprazole contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile.

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

## **Domperidone**

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g. in patients with gastrointestinal hemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment.
- 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.
- Co-administration with QT-prolonging drugs.
- co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)

### 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.

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. 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 children. 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.

Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic 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 in infants

Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

#### Renal impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, 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.

### **4.5 DRUG INTERACTION**

#### **Omeprazole**

##### Effects of omeprazole on the pharmacokinetics of other active substances

##### Active substances with pH dependent absorption

The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

##### *Nelfinavir, atazanavir*

The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole.

Concomitant administration of omeprazole with nelfinavir is contraindicated. Co-administration of omeprazole (40 mg once daily) reduced mean nelfinavir exposure by ca. 40% and the mean exposure of the pharmacologically active metabolite M8 was reduced by ca. 75–90%. The interaction may also involve CYP2C19 inhibition.

Concomitant administration of omeprazole with atazanavir is not recommended. Concomitant administration of omeprazole (40 mg once daily) and atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a 75% decrease of the atazanavir exposure. Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once daily) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared to atazanavir 300 mg/ritonavir 100 mg once daily.

### *Digoxin*

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10%. Digoxin toxicity has been rarely reported. However caution should be exercised when omeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should be then be reinforced.

### *Clopidogrel*

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and omeprazole (80 mg p.o. daily) resulting in a decreased exposure to the active metabolite of clopidogrel by an average of 46% and a decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 16%.

Inconsistent data on the clinical implications of a PK/PD interaction of omeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

### *Other active substances*

The absorption of posaconazole, erlotinib, ketoconazole and itraconazole is significantly reduced and thus clinical efficacy may be impaired. For posaconazole and erlotinib concomitant use should be avoided.

### *Active substances metabolised by CYP2C19*

Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

### *Cilostazol*

Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C<sub>max</sub> and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

### *Phenytoin*

Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

### *Unknown mechanism*

#### *Saquinavir*

Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

#### *Tacrolimus*

Concomitant administration of omeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal

function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

#### *Methotrexate*

When given together with proton-pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of omeprazole may need to be considered.

#### Effects of other active substances on the pharmacokinetics of omeprazole

##### *Inhibitors of CYP2C19 and/or CYP3A4*

Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment resulted in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

##### *Inducers of CYP2C19 and/or CYP3A4*

Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

#### **Domperidone**

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* 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).

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

- protease inhibitors
- systemic azole antifungals

- Some macrolides (erythromycin, clarithromycin, telithromycin).

**Concomitant use of the following substances is not recommended**

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

**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.

## 4.6 USE IN SPECIAL POPULATION

### **Omeprazole**

#### Pregnancy

Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the fetus/newborn child. Omeprazole can be used during pregnancy.

#### Breast-feeding

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

#### Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

### **Domperidone**

#### 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. Domperidone 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**

### **Omeprazole**

Omeprazole is not likely to affect the ability to drive or use machines. Adverse drug reactions such as dizziness and visual disturbances may occur. If affected, patients should not drive or operate machinery.

### **Domperidone**

Domperidone has no or negligible influence on the ability to drive and use machines.

## **4.8 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

### **Omeprazole**

#### Summary of the safety profile

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

#### Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related. Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data).

<b>SOC/freque</b>	<b>Adverse reaction</b>
<b>Blood and lymphatic system disorders</b>	
Rare:	Leukopenia, thrombocytopenia
Very rare:	Agranulocytosis, pancytopenia
<b>Immune system disorders</b>	
Rare:	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
<b>Metabolism and nutrition disorders</b>	
Rare:	Hyponatraemia



Not known:	Hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
<b>Psychiatric disorders</b>	
Uncommon:	Insomnia
Rare:	Agitation, confusion, depression
Very rare:	Aggression, hallucinations
<b>Nervous system disorders</b>	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, somnolence
Rare:	Taste disturbance
<b>Eye disorders</b>	
Rare:	Blurred vision
<b>Ear and labyrinth disorders</b>	
Uncommon:	Vertigo
<b>Respiratory, thoracic and mediastinal disorders</b>	
Rare:	Bronchospasm
<b>Gastrointestinal disorders</b>	
Common:	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
Rare:	Dry mouth, stomatitis, gastrointestinal candidiasis
Not known:	Microscopic colitis
<b>Hepatobiliary disorders</b>	
Uncommon:	Increased liver enzymes
Rare:	Hepatitis with or without jaundice
Very rare:	Hepatic failure, encephalopathy in patients with pre-existing liver disease
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon:	Dermatitis, pruritus, rash, urticaria
Rare:	Alopecia, photosensitivity
Very rare:	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)
Not known:	Subacute cutaneous lupus erythematosus
<b>Musculoskeletal and connective tissue disorders</b>	
Uncommon:	Fracture of the hip, wrist or spine
Rare:	Arthralgia, myalgia
Very rare:	Muscular weakness

<b>Renal and urinary disorders</b>	
Rare:	Interstitial nephritis
Not known:	Acute kidney injury
<b>Reproductive system and breast disorders</b>	
Very rare:	Gynaecomastia
<b>General disorders and administration site conditions</b>	
Uncommon:	Malaise, peripheral oedema
Rare:	Increased sweating

#### Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long-term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

#### **Domperidone**

##### 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 Domperidone (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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); 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
<b>Immune system disorders</b>			Anaphylactic reaction (including anaphylactic shock)
<b>Psychiatric disorders</b>		Loss of libido Anxiety	Agitation Nervousness
<b>Nervous system disorders</b>		Somnolence Headache	Convulsion Extrapyramidal disorder

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

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.

#### Paediatric population

Extrapyramidal disorder occurs primarily in neonates and infants other central nervous system-related effects of convulsion and agitation also are primarily reported in infants and children.

## 4.9 OVERDOSE

### **Omeprazole**

There is limited information available on the effects of overdoses of omeprazole in humans. In the literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.

The symptoms described have been transient, and no serious outcome has been reported.

The rate of elimination was unchanged (first order kinetics) with increased doses.

Treatment, if needed, is symptomatic.

## **Domperidone**

### *Symptoms*

Overdose has been reported primarily in infants and children. Symptoms of overdose 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**

#### **Omeprazole**

Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitors, ATC code: A02BC01

#### Mechanism of action

Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing.

Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H<sup>+</sup> K<sup>+</sup>-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

#### Pharmacodynamic effects

All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion.

#### Effect on gastric acid secretion

Oral dosing with omeprazole once daily provides for rapid and effective inhibition of daytime and night-time gastric acid secretion with maximum effect being achieved within 4 days of treatment. With omeprazole 20 mg, a mean decrease of at least 80% in 24-hour intragastric acidity is then maintained in duodenal ulcer patients, with the mean decrease in peak acid output after pentagastrin stimulation being about 70% 24 hours after dosing.

Oral dosing with omeprazole 20 mg maintains an intragastric pH of  $\geq 3$  for a mean time of 17 hours of the 24-hour period in duodenal ulcer patients.

As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalizes acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease.

The inhibition of acid secretion is related to the area under the plasma concentration-time curve (AUC) of omeprazole and not to the actual plasma concentration at a given time.

No tachyphylaxis has been observed during treatment with omeprazole.

#### Effect on *H. pylori*

*H. pylori* is associated with peptic ulcer disease, including duodenal and gastric ulcer disease. *H. pylori* is a major factor in the development of gastritis. *H. pylori* together with gastric acid are major factors in the development of peptic ulcer disease. *H. pylori* is a major factor in the development of atrophic gastritis which is associated with an increased risk of developing gastric cancer.

Eradication of *H. pylori* with omeprazole and antimicrobials is associated with, high rates of healing and long-term remission of peptic ulcers.

Dual therapies have been tested and found to be less effective than triple therapies. They could, however, be considered in cases where known hypersensitivity precludes use of any triple combination.

#### Other effects related to acid inhibition

During long-term treatment gastric glandular cysts have been reported in a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients (both children and adults) during long term treatment with omeprazole. The findings are considered to be of no clinical significance.

#### Paediatric population

In a non-controlled study in children (1 to 16 years of age) with severe reflux oesophagitis, omeprazole at doses of 0.7 to 1.4 mg/kg improved oesophagitis level in 90% of the cases and significantly reduced reflux symptoms. In a single-blind study, children aged 0–24 months with clinically diagnosed gastro-oesophageal reflux disease were treated with 0.5, 1.0 or 1.5 mg omeprazole/kg. The frequency of vomiting/regurgitation episodes decreased

by 50% after 8 weeks of treatment irrespective of the dose.

#### Eradication of *H. pylori* in children

A randomised, double blind clinical study (Héliot study) concluded that omeprazole in combination with two antibiotics (amoxicillin and clarithromycin), was safe and effective in the treatment of *H. pylori* infection in children age 4 years old and above with gastritis:

*H. pylori* eradication rate: 74.2% (23/31 patients) with omeprazole + amoxicillin + clarithromycin versus 9.4% (3/32 patients) with amoxicillin + clarithromycin. However, there was no evidence of any clinical benefit with respect to dyspeptic symptoms. This study does not support any information for children aged less than 4 years

### **Domperidone**

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.

## **5.2 PHARMACOKINETIC PROPERTIES**

### Absorption

Omeprazole and omeprazole magnesium are acid labile and are therefore administered orally as enteric-coated granules in capsules or tablets. Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. Concomitant intake of food has no influence on the bioavailability. The systemic availability

(bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

### Distribution

The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

### Biotransformation

Omeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulfone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19. However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates. In addition, omeprazole lacks an inhibitory effect on the main CYP enzymes.

Approximately 3% of the Caucasian population and 15-20% of Asian populations lack a functional CYP2C19 enzyme and are called poor metabolisers. In such individuals the metabolism of omeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 20 mg omeprazole, the mean AUC was 5 to 10 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were also higher, by 3 to 5 times. These findings have no implications for the posology of omeprazole.

### Elimination

The plasma elimination half-life of omeprazole is usually shorter than one hour both after single and repeated oral once-daily dosing. Omeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

### Linearity/non-linearity

The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulfone).

No metabolite has been found to have any effect on gastric acid secretion.

### Special populations

#### *Hepatic impairment*

The metabolism of omeprazole in patients with liver dysfunction is impaired, resulting in an increased AUC. Omeprazole has not shown any tendency to accumulate with once daily dosing.

### Renal impairment

The pharmacokinetics of omeprazole, including systemic bioavailability and elimination rate, are unchanged in patients with reduced renal function.

### Elderly

The metabolism rate of omeprazole is somewhat reduced in elderly subjects (75-79 years of age).

### Paediatric population

During treatment with the recommended doses to children from the age of 1 year, similar plasma concentrations were obtained as compared to adults. In children younger than 6 months, clearance of omeprazole is low due to low capacity to metabolise omeprazole.

## **Domperidone**

### Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The C<sub>max</sub> 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 gastrointestinal 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 drug is taken after a meal.

### Distribution

Oral domperidone does not appear to accumulate or 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 C<sub>max</sub> 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 C<sub>max</sub> 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.

### Renal impairment

In subjects with severe renal insufficiency (creatinine clearance <30ml/min/1.73m<sup>2</sup>) the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are 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.

## **6. NON-CLINICAL PROPERTIES**

### **6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY**

#### **Omeprazole**

Gastric ECL-cell hyperplasia and carcinoids, have been observed in life-long studies in rats treated with omeprazole. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. Similar findings have been made after treatment with H<sub>2</sub>-receptor antagonists, proton pump inhibitors and after partial fundectomy. Thus, these changes are not from a direct effect of any individual active substance.

#### **Domperidone**

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 IC<sub>50</sub> values inhibiting currents through IK<sub>r</sub> ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg 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 (10 mg administered 3 times a day) by 45-fold. Safety margins in *in vitro* pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg 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 a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg 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

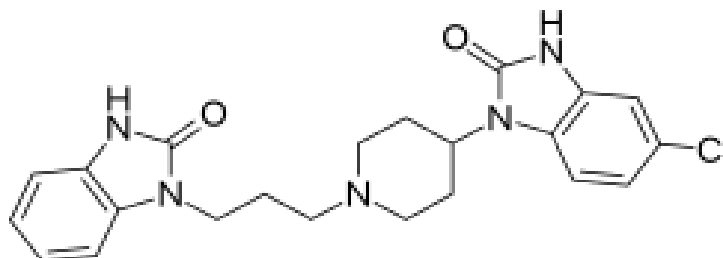
effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

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 human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

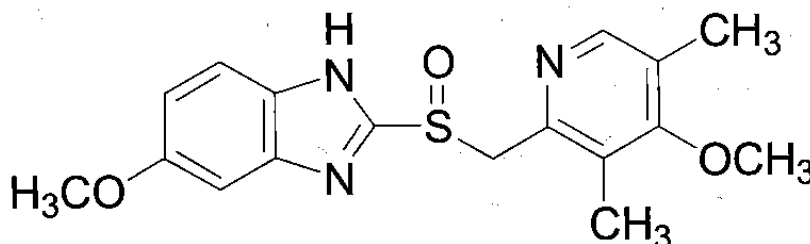
## 7. DESCRIPTION

Domperidone is 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one. Having molecular weight 425.9 and its empirical formula is C<sub>22</sub>H<sub>24</sub>ClN<sub>5</sub>O<sub>2</sub>. The structural formula is:



Domperidone is a white or almost white powder. Soluble in dimethylformamide, slightly soluble in ethanol (95 percent) and in methanol; practically insoluble in water.

Omeprazole is 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-pyridin-2-yl)methyl]sulfinyl]-1H-benzimidazole. Having molecular weight 345.4 and its empirical formula is C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S. The structural formula is:



Omeprazole is a white or almost white powder. Freely soluble in dichloromethane and in chloroform; soluble in ethanol (95 per cent) and in methanol; very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides.

### Product Description:

Domstal RD is Violet/White hard gelatin capsules printed with “DOMSTAL-RD” and Torrent logo (square emblem only) on the shells of the capsules, containing orange coloured pellets and white to off-white pellets.

OTHER INACTIVE INGREDIENTS are HYDROXY PROPYL METHYL CELU., MAGNESIUM STEARATE, FERRIC OXIDE YELLOW, FERRIC OXIDE RED, TALC,

ETHYL CELLULOSE, METHANOL, METHYLENE CHLORIDE, SUGAR GLOBULE, TITANIUM DIOXIDE, Met.Acid&Eth.Acr.co., PEG -6000.

## **8. PHARMACEUTICAL PARTICULARS**

### **8.1 Incompatibilities**

Not available

### **8.2 Shelf Life**

Do not use later than date of expiry

### **8.3 Packaging Information**

Domstal RD is available in Blister pack of 15 Capsules.

### **8.4 Storage and handling instructions**

STORE BELOW 25 °C, PROTECTED FROM LIGHT AND MOISTURE.

## **9. PATIENT COUNSELLING INFORMATION**

### **DOMSTAL RD**

Omeprazole and Domperidone Capsules.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

#### **What is in this leaflet?**

### **9.1. What DOMSTAL RD is and what it is used for**

DOMSTAL RD Capsules contain Omeprazole 20mg (as enteric coated pellets) and Domperidone Maleate 10mg respectively. DOMSTAL RD used in the treatment of Gastroesophageal Reflux Disease (GERD) not responding to Omeprazole alone.

### **9.2. What you need to know before you take DOMSTAL RD.**

#### **Do not take DOMSTAL RD Capsules if**

- You are allergic (hypersensitive) to Omeprazole/domperidone or any of the other ingredients. Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- You have a tumour of the pituitary gland (prolactinoma)
- You have a blockage or tear in your intestines
- You have black, tarry bowel motions (stools) or notice blood in your bowel motions. This could be a sign of bleeding in the stomach or intestines.
- You have a moderate or severe liver disease.
- Your ECG (electrocardiogram) shows a heart problem called “prolonged QT corrected interval”.

- You have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure).
- You have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood.
- You are taking certain medicines
- You are taking HIV protease inhibitors such as atazanavir, nelfinavir (for the treatment of HIV-infection)

Do not take **DOMSTAL RD** if any of the above applies to you. If you are not sure, talk to your doctor before taking **DOMSTAL RD**.

## **Warnings and precautions**

### **Omeprazole**

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients. Omeprazole like other proton pump inhibitors (PPIs) must not be used concomitantly with nelfinavir.

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.

Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like omeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

### Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

#### Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, omeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Omeprazole contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile.

As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

### **Domperidone**

Domperidone is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g. in patients with gastrointestinal hemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment.
- 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.
- Co-administration with QT-prolonging drugs.
- co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)

#### 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.

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. 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 children. 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.

Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic 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 in infants

Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Overdosing may cause extrapyramidal symptoms in children, but other causes should be taken into consideration.

#### Renal impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, 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.

### **9.3. How to take DOMSTAL RD.**

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor if you are not sure.

The recommended dose is one capsule a day.

You should take this medicine for at least 2–3 consecutive days. Stop taking when you are completely symptom-free. You may experience relief from your acid reflux and heartburn symptoms after just one day of treatment with this medicine, but this medicine is not meant to bring immediate relief.

If you have no symptom-relief after taking this medicine for 2 weeks continuously, consult your doctor.

Take the capsule before a meal, at the same time every day.

You should swallow the capsule whole with some water.

Do not chew or break the capsule

#### **If you forget to take DOMSTAL RD**

If you forget to take a dose of DOMSTAL RD, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

#### **If you stop taking DOMSTAL RD**

Should your doctor decide to stop your DOMSTAL RD treatment, he/she will instruct you about the gradual withdrawal of DOMSTAL RD

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### **9.4. Possible side effects**

#### **Omeprazole**

##### Summary of the safety profile

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

##### Tabulated list of adverse reactions

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related.

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency categories are defined according to the following convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders:** Leukopenia, thrombocytopenia, Agranulocytosis, pancytopenia

**Immune system disorders:** Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

**Nervous system disorders:** Headache, Dizziness, paraesthesia, Taste disturbance

**Eye disorders:** Blurred vision

**Ear and labyrinth disorders:** Vertigo

**Respiratory, thoracic and mediastinal disorders:** Bronchospasm

**Gastrointestinal disorders:** Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign), Dry mouth, stomatitis, gastrointestinal candidiasis and Microscopic colitis.

**Hepatobiliary disorders:** Increased liver enzymes, Hepatitis with or without jaundice, Hepatic failure, encephalopathy in patients with pre-existing liver disease

**Skin and subcutaneous tissue disorders:** Dermatitis, pruritus, rash, urticarial, Alopecia, photosensitivity, Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and Subacute cutaneous lupus erythematosus.

**Musculoskeletal and connective tissue disorders:** Fracture of the hip, wrist or spine, Arthralgia, myalgia, Muscular weakness.

**Renal and urinary disorders:** Interstitial nephritis

**Reproductive system and breast disorders:** Gynaecomastia

**General disorders and administration site conditions:** Malaise, peripheral oedema, Increased sweating

#### Paediatric population

The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long-term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long-term data regarding the effects of omeprazole treatment on puberty and growth.

#### **Domperidone**

##### 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 Domperidone (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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), Where frequency cannot be estimated from clinical trials data, it is recorded as “Not known”.

**Immune system disorders:** Anaphylactic (including Anaphylactic shock)

**Psychiatric disorders:** Loss of libido, Anxiety, Agitation Nervousness

**Nervous system disorders:** Somnolence, Headache, Convulsion Extrapyramidal disorder

**Eye disorders:** Oculogyric crisis

**Cardiac disorders:** Ventricular arrhythmias, Sudden cardiac death, QTc prolongation  
Torsade de Pointes

**Gastrointestinal disorders:** Dry mouth, Diarrhoea

**Skin and subcutaneous tissue disorder:** Rash Pruritus, Urticaria Angioedema

**Renal and urinary disorder:** 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

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.

#### Paediatric population

Extrapyramidal disorder occurs primarily in neonates and infants other central nervous system-related effects of convulsion and agitation also are primarily reported in infants and children.

### **9.5. How to store DOMSTAL RD.**

STORE BELOW 25 °C, PROTECTED FROM LIGHT AND MOISTURE.

### **10. Details of manufacturer**

Torrent Pharmaceuticals Ltd  
Vill. Bhud & Makhnu Majra,



Teh. Baddi -173 205, Dist. Solan (H.P.), INDIA.

**11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE**

Torrent Pharmaceuticals Ltd  
Mfg. Lic. No. MNB/05/183 issued on 11.10.2018

**12. DATE OF REVISION**

**MARKETED BY**



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road, Ahmedabad-380 009, INDIA

**IN/DOMSTAL RD 10, 20mg/Mar-22/06/PI**