IZRA D

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

Abbreviated prescribing information for IZRA D (Esomeprazole Magnesium and Domperidone Sustained Release Capsules) [Please refer the complete prescribing information available at www.torrentpharma.com]

MECHANISM OF ACTION: *Esomeprazole:* Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell. Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40mg and leads to inhibition of gastric acid secretion. *Domperidone:* Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially 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.

INDICATION: It is indicated for the treatment of adult patients with gastroesophagal reflux disease (GERD) not responding to esomeprazole alone.

DOSAGE AND ADMINISTRATION: The dose of IZAR D must be taken as prescribe by Physician. The capsules should be swallowed whole with half a glass of water. The capsules must not be chewed, crushed or opened.

CONTRAINDICATION: *Esomeprazole:*Hypersensitivity to the active substance, to substituted benzimidazoles or to any of the excipients. Esomeprazole should not be used concomitantly with nelfinavir. *Domperidone:* It 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 gastro-intestinal 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, at the exception of apomorphine, Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

WARNINGS & PRECAUTIONS: *Esomeprazole:* Long term use, Helicobacter pylori eradication, Gastrointestinal infections, Absorption of vitamin B12, Hypomagnesaemia, Risk of fracture, Subacute cutaneous lupus erythematosus (SCLE), Co-administration of esomeprazole with atazanavir is not recommended and Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements. *Domperidone:* Cardiovascular effects, use with apomorphine, Use in infants and with Renal impairment.

DRUG INTERACTIONS: *Esomeprazole:* Effects of esomeprazole on the pharmacokinetics of other drugs like Protease inhibitors, Methotrexate, Tacrolimus, Medicinal products metabolised by CYP2C19, Diazepam, Phenytoin, Voriconazole, Cilostazol, Cisapride, Warfarin, Clopidogrel, Amoxicillin and quinidine, Naproxen or rofecoxib, Medicinal products which inhibit CYP2C19 and/or CYP3A4 and Medicinal products which induce CYP2C19 and/or CYP3A4. *Domperidone:* QTc prolonging medicinal products like 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) and 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). Concomitant use of the following substances is not recommended- Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

ADVERSE REACTIONS: *Serious allergic reactions (rare: may affect up to 1 in 1,000 people):* Hypersensitivity reactions, so-called anaphylactic reactions, anaphylactic shock and angioedema. Typical symptoms are: swelling of the face, lips, mouth, tongue and/or throat, which may cause difficulty in swallowing or breathing, hives (nettle rash), severe dizziness with very fast heartbeat and heavy sweating. *Serious skin reactions (frequency not known:* frequency cannot be estimated from the available data): rash with swelling, blistering or peeling of the skin, losing skin and bleeding around eyes, nose, mouth or genitals and rapid deterioration of your general health, or rash when exposed to the sun. *Other serious reactions (frequency not known):* yellowing of the skin and eyes (due to severe liver damage), or kidney problems such as painful urination and lower back pain with fever. – *Common (may affect up to 1 in 10 people):* Benign polyps in the stomach. *Uncommon side effects (may affect up to 1 in 100 people):* headache; dizziness; diarrhoea; feeling sick; vomiting; bloating and flatulence (wind); constipation; dry mouth; bellyache and discomfort; skin rash or hives; itching; feeling weak, exhausted or generally unwell; sleep disorders; increase in liver enzymes in a blood test; fracture in the hip, wrist or spine. *Rare side effects:* distortion or complete lack of the sense of taste; disturbances in vision such as blurred vision; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities; depression; increased bilirubin and fat levels in blood (seen in blood test); breast enlargement in males; acute kidney injury; high fever and a sharp drop in circulating granular white blood cells (seen in blood test). *Very rare side effects (may affect up to 1 in 10,000 people):* disorientation; reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; reduction in the number of white blood cells, which may lead to more frequent infections; coexisting abnormal reduction in the number of red and white blood cells, as well as platelets (seen in blood tests), *Frequency not known:* hallucination; confusion (especially in patients with a history of these symptoms); decreased level of sodium in blood, decreased level of magnesium in blood, rash, possibly with pain in the joints.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

IN/IZRA D 20+30 and 40+30 mg/Feb/22/02/PI

(Additional information is available on request)