SUMMARY PRODUCT CHARACTERISTICS **ZOLETRI DSR** **Rabeprazole Sodium (EC) and Domperidone (SR) Capsules**	Mars Remedies Pvt. Ltd.

1. NAME OF THE MEDICINAL PRODUCT

1.1Name of the Medicinal Product
ZOLETRI DSR
Rabeprazole Sodium (EC) and Domperidone (SR) Capsules

1.2 Strength
20 + 30 mg

1.3 Pharmaceutical Form
Capsule, Oral dosage form

2. QUALITATIVEANDQUANTITATIVECOMPOSITION
Each hard gelatin capsule contains:
Rabeprazole Sodium 20 mg
(As enteric coated pellets)
Domperidone BP 30 mg
(As Sustained release pellets)
Approved colour used in empty hard gelatin capsule shells.

3. PHARMACEUTICAL FORM
Capsules
Pink / Clear transparent capsule of size "2" containing orange and brown coloured spherical pellets.

4.CLINICAL PARTICULARS
4.1.Therapeutic Indications
ZOLETRI DSR is an anti-ulcerant and anti-emetic combination that addresses acid-reflux issues, different types of ulcers, nausea and vomiting. Rabeprazole is a proton pump inhibitor, while domperidone is a dopamine antagonist. Studies show that the combination of rabeprazole and domperidone effectively addresses gastroesophageal reflux disorder than rabeprazole alone.

4.2. Posology and method of administration
Take this medicine in the dose and duration as advised by your doctor. Swallow it as a whole. Do not chew, crush or break it. ZOLETRI DSR is to be taken empty stomach.

4.3. Contra-indications
Hypersensitivity to Rabeprazole+Domperidone capsule is a contraindication.
In addition, Rabeprazole + Domperidone capsule should not be used if you have the following conditions:

- Breastfeeding
- Co-administration with potent CYP3A4 inhibitors
- Concomitant use with medicines that prolong the QT interval
- Congestive heart failure
- Hypersensitivity
- Hypersensitivity to domperidone
- Moderate or severe hepatic impairment

- Patients with significant electrolyte disturbances
- Pregnant
- Presence of gastrointestinal haemorrhage

4.4. Special warnings and special precautions for use

Before using ZOLETRI DSR, inform your doctor about your current list of medications, over the counter products (e.g. vitamins, herbal supplements, etc.), allergies, pre-existing diseases, and current health conditions (e.g. pregnancy, upcoming surgery, etc.). Some health conditions may make you more susceptible to the side-effects of the drug. Take as directed by your doctor or follow the direction printed on the product insert. Dosage is based on your condition. Tell your doctor if your condition persists or worsens. Important counseling points are listed below.

- Avoid driving or operating machinery
- Concurrent use with QT prolongating agents
- Discontinue use if experiencing signs or symptoms associated with cardiac arrhythmia
- Helps treat GERD or reflux
- May increase risk for lupus
- May increase risk for osteoporosis
- Notify doctor if taking atazanavir, nelfinavir, or rilpivirine
- Older patients
- Patients with bradycardia
- Patients with cardiac diseases

4.5. Interactions with other Drug products and other forms of interaction

The following is a list of possible side-effects that may occur from all constituting ingredients of ZOLETRI DSR. This is not a comprehensive list. These side-effects are possible, but do not always occur. Some of the side-effects may be rare but serious. Consult your doctor if you observe any of the following side-effects, especially if they do not go away.

- Nausea
- Pruritus
- Abdominal pain
- Sleeplessness
- Constipation
- Headache
- Somnolence
- Akathisia
- Diarrhea
- Rash

4.6. Pregnancy and lactation

Pregnancy

There are no data on the safety of rabeprazole in human pregnancy.

Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to rabeprazole sodium, although low foeto-placental transfer occurs in rats. Zoletri Dsr is contraindicated during pregnancy.

Breast feeding

It is not known whether rabeprazole sodium is excreted in human breast milk. No studies in breast-feeding women have been performed. Rabeprazole sodium is however excreted in rat mammary secretions. Therefore Zoletri Dsr should not be used during breast feeding.

4.7. Effects on ability to drive and use machines

Based on the pharmacodynamic properties and the adverse events profile, it is unlikely that Zoletri DSR would cause an impairment of driving performance or compromise the ability to use machinery. If however, alertness is impaired due to somnolence, it is recommended that driving and operating complex machinery be avoided.

4.8. ADVERSE REACTIONS

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketing experience.

Frequencies are defined as: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (>1/10,000, <1/1000) very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations	Infection				
Blood and the lymphatic system disorders			Neutropenia Leucopenia Thrombocytopenia Leucocytosis		
Immune system disorders			Hypersensitivity[1,2]		
Metabolism and nutrition disorders			Anorexia		Hyponatremia Hypomagnesaemia[4]
Psychiatric disorders	Insomnia	Nervousness	Depression		Confusion
Nervous system disorders	Headache Dizziness	Somnolence			
Eye disorders			Visual disturbance		
Vascular disorders					Peripheral Oedema
Respiratory, thoracic and mediastinal disorders	Cough Pharyngitis Rhinitis	Bronchitis Sinusitis			
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Abdominal pain Constipation Flatulence Fundic Gland Polyps (Benign)	Dyspepsia Dry mouth Eructation	Gastritis Stomatitis Taste disturbance		Microscopic colitis
Hepato-biliary disorders			Hepatitis Jaundice Hepatic encephalopathy[3]		
Skin and subcutaneous tissue disorders		Rash Erythema[2]	Pruritus Sweating Bullous reactions[2]	Erythema multiforme, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS)	Subacute cutaneous lupus erythematosus[4]

Musculoskeletal connective tissue and bone disorders	Non-specific pain Back pain	Myalgia Leg cramps Arthralgia Fracture of the hip, wrist or spine[4]			
Renal and urinary disorders		Urinary tract infection	Interstitial nephritis		
Reproductive system and breast disorders					Gynaecomastia
General disorders and administration site conditions	Asthenia Influenza like illness	Chest pain Chills Pyrexia			
Investigations		Increased hepatic enzymes[3]	Weight increased		

1: Includes facial swelling, hypotension and dyspnoea
2: Erythema, bullous reactions and hypersensitivity reactions have usually resolved after discontinuation of therapy.
3: Rare reports of hepatic encephalopathy have been received in patients with underlying cirrhosis. In treatment of patients with severe hepatic dysfunction the prescriber is advised to exercise caution when treatment with Zoletri Dsr is first initiated in such patients

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.

4.9 Overdose
Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Alimentary tract and metabolism, Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), PPIs,
ATC code: A02B C04
ATC code: A03FA03
ZOLETRI DSR is a combination of two medicines: Domperidone and Rabeprazole.
Domperidone is a prokinetic which works on the upper digestive tract to increase the movement of the stomach and intestines, allowing the food to move more easily through the stomach.
Rabeprazole is a proton pump inhibitor (PPI) which works by reducing the amount of acid in the stomach which helps in the relief of acid-related indigestion and heartburn.
Rabeprazole is a substituted benzimidazole and it works as a proton pump inhibitor (PPI). After the administration, rabeprazole is absorbed by the parietal cells. Rabeprazole is activated in the acidic environment only. The activated rabeprazole binds to the H+/ K+ ATPase system present on the parietal cells and prevents the inward movement of H+ ions into the stomach and inhibits the gastric acid production.
Domperidone is a strong anti-emetic and anti-ulcerant agent that controls nausea and vomiting along with the suppression of acid-reflux. On peripheral levels, it increases the lower esophageal

pressure, improves the motility in the upper GI tract or peristalsis. Centrally, domperidone acts as an antagonist of D2 and D3 dopamine receptors in the area postrema of the brain where the chemoreceptor trigger zone for nausea and vomiting is present.

5.2PharmacokineticProperties

Zoletri DSR is an e formulation of Rabeprazole sodium and domepridone. This presentation is necessary because rabeprazole is acid-labile.

Absorption of rabeprazole therefore begins only after the leaves the stomach. Absorption is rapid, with peak plasma levels of rabeprazole occurring approximately 3.5 hours after a dose. Peak plasma concentrations (Cmax) of rabeprazole and AUC are linear over the dose range of 10 mg to 40 mg. Absolute bioavailability of an oral dose (compared to intravenous administration) is about 52% due in large part to pre-systemic metabolism. Additionally the bioavailability does not appear to increase with repeat administration. In healthy subjects the plasma half-life is approximately one hour (range 0.7 to 1.5 hours), and the total body clearance is estimated to be 283 ± 98 ml/min. There was no clinically relevant interaction with food. Neither food nor the time of day of administration of the treatment affect the absorption of rabeprazole sodium.

Distribution

Rabeprazole is approximately 97% bound to human plasma proteins.

Metabolism and excretion

Rabeprazole sodium, as is the case with other members of the PPI class of compounds, is metabolised through the cytochrome P450 (CYP450) hepatic drug metabolising system. In vitro studies with human liver microsomes indicated that rabeprazole sodium is metabolised by isoenzymes of CYP450 (CYP2C19 and CYP3A4). In these studies, at expected human plasma concentrations rabeprazole neither induces nor inhibits CYP3A4; and although in vitro studies may not always be predictive of in vivo status these findings indicate that no interaction is expected between rabeprazole and cyclosporin. In humans the thioether (M1) and carboxylic acid (M6) are the main plasma metabolites with the sulphone (M2), desmethyl-thioether (M4) and mercapturic acid conjugate (M5) minor metabolites observed at lower levels. Only the desmethyl metabolite (M3) has a small amount of anti-secretory activity, but it is not present in plasma.

Following a single 14C labelled oral dose of rabeprazole sodium, no unchanged drug was excreted in the urine. Approximately 90% of the dose was eliminated in urine mainly as the two metabolites: a mercapturic acid conjugate (M5) and a carboxylic acid (M6), plus two unknown metabolites. The remainder of the dose was recovered in faeces.

Gender

Adjusted for body mass and height, there are no significant gender differences in pharmacokinetic parameters following a single dose of rabeprazole.

Renal dysfunction

In patients with stable, end-stage, renal failure requiring maintenance haemodialysis (creatinine clearance ≤5ml/min/1.73 m2), the disposition of rabeprazole was very similar to that in healthy volunteers. The AUC and the Cmax in these patients was about 35% lower than the corresponding parameters in healthy volunteers. The mean half-life of rabeprazole was 0.82 hours in healthy volunteers, 0.95 hours in patients during haemodialysis and 3.6 hours post dialysis. The clearance of the drug in patients with renal disease requiring maintenance haemodialysis was approximately twice that in healthy volunteers.

Hepatic dysfunction

Following a single dose of rabeprazole to patients with chronic mild to moderate hepatic impairment the AUC doubled and there was a 2-3 fold increase in half-life of rabeprazole

compared to the healthy volunteers. However, following a dose daily for 7 days the AUC had increased to only 1.5-fold and the Cmax to only 1.2-fold. The half-life of rabeprazole in patients with hepatic impairment was 12.3 hours compared to 2.1 hours in healthy volunteers. The pharmacodynamic response (gastric pH control) in the two groups was clinically comparable.
Older people
Elimination of rabeprazole was somewhat decreased in older people. Following 7 days of daily dosing with of rabeprazole sodium, the AUC approximately doubled, the Cmax increased by 60% and t½ increased by approximately 30% as compared to young healthy volunteers. However there was no evidence of rabeprazole accumulation.
CYP2C19 polymorphism
Following a daily dose of rabeprazole for 7 days, CYP2C19 slow metabolisers, had AUC and t½ which were approximately 1.9 and 1.6 times the corresponding parameters in extensive metabolisers whilst Cmax had increased by only 40%.

5.3. Preclinical safety data
Non-clinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that make concerns for human safety negligible in respect of animal data.
Studies on mutagenicity gave equivocal results. Tests in mouse lymphoma cell line were positive, but in vivo micronucleus and in vivo and in vitro DNA repair tests were negative. Carcinogenicity studies revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients
No excipients are used in formulation

6.2. Incompatibilities
None

6.3.Shelflife
36Months.

6.4 Special precautions for storage
Store below above 30 ^{o}C.
Protect from light &moisture

6.5. Nature and contents of container
Aluminium - Aluminium Blister Pack
10 Capsules are blister packed with Aluminium - Aluminium foil; such 1 blisters are packed in one carton pack. Pack size: 1 x 10 Capsules (i.e. 10 Capsules) in one carton box along with packing leaflet.

6.6. Special precautions for disposal and other handling
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7.0 Registrant
Eastleigh Pharmaceuticals Co. Ltd
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8.0 Manufacturer
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9.0 Date of Publication or Revision
Last revised on Dec 2020

10. DOSIMETRY (IF APPLICABLE)
Not Applicable

11. Instructions for Preparation of Radiopharmaceuticals (If Applicable):
Not Applicable