1. Name of the Medicinal Product:

Product Name: **Limzer**
(Enteric Coated Omeprazole 20mg & Domperidone Sustained Release 30mg capsules)

2. Qualitative and quantitative composition

Qualitative Declaration:

Qualitative Declaration:

Name of Ingredients	Specification
Omeprazole*	BP/Ph. Eur.
Non Pareil seeds (18-20#) MgCO3 and HPMC Coated $	In House
Hypromellose E 15	BP/Ph. Eur.
Hypromellose E 5 (5cps)	BP/Ph. Eur.
Purified Talc	BP/Ph. Eur.
Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion	USP
Sodium hydroxide	BP/Ph. Eur.
Titanium Dioxide	BP/Ph. Eur.
Glycerol monostearate 40 - 55	Ph. Eur.
Polysorbate 80	BP/Ph. Eur.
Magnesium stearate	BP/Ph. Eur.
Hypromellose Pthalate (HP 55)	BP/Ph. Eur.
Dibutyl sebacate	USP
Methyl Alcohol^	USP
Dichloromethane ^	BP/Ph. Eur.
Purified Water ^	USP/Ph. Eur
Sub Total 1	
Domperidone	BP/Ph. Eur.

Non pareil seeds (18- 20 #) $	INH
Colloidal Anhydrous Silica	BP/Ph. Eur.
Hypromellose E 5(5cps)	BP/Ph. Eur.
Purified Talc	BP/Ph. Eur.
Ethyl cellulose (10 cps)	USP
Triacetin	USP-NF
Ferric oxide (yellow)	USP-NF
Ferric oxide (red) (PH/IN-919)	USP-NF
Titanium Dioxide	BP/Ph. Eur.
Methyl alcohol ^	USP
Dichloromethane ^	BP/Ph. Eur.
Purified Water ^	USP/Ph. Eur.

Quantitative Declaration:

Name of Ingredients	Specification	mg/cap	function
Enteric Coated Omeprazole Pellets 22.22% w/w			
Omeprazole*	BP/Ph. Eur.	#20.00	Proton Pump Inhibitor
Non Pareil seeds (18-20#) $MgCO_3$ and HPMC Coated $	In House	32.60	Substrate for layering
Hypromellose E 15	BP/Ph. Eur.	3.10	Binder
Hypromellose E 5 (5cps)	BP/Ph. Eur.	6.15	Binder
Purified Talc	BP/Ph. Eur.	4.56	Binder
Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion	USP	◆15.33	Enteric Coating Polymer
Sodium hydroxide	BP/Ph. Eur.	2.72	Alkalizing Agent
Titanium Dioxide	BP/Ph. Eur.	0.46	Opacifier
Glycerol monostearate 40 - 55	Ph. Eur.	0.76	Anti-tack agent
Polysorbate 80	BP/Ph. Eur.	0.08	Solubilizer
Magnesium stearate	BP/Ph. Eur.	1.38	Lubricant
Hypromellose Pthalate (HP 55)	BP/Ph. Eur.	2.61	Release modifying Agent
Dibutyl sebacate	USP	0.26	Plasticizer
Methyl Alcohol^	USP	56.51	Solvent
Dichloromethane ^	BP/Ph. Eur.	84.81	Solvent
Purified Water ^	USP/Ph. Eur	266.46	Solvent
Sub Total 1		**90.00**	
Domperidone SR Pellets 40 % w/w			
Domperidone	BP/Ph. Eur.	#30.00	Antiemetic
Non pareil seeds (18- 20 #) $	INH	36.03	Substrate for layering
Colloidal Anhydrous Silica	BP/Ph. Eur.	0.48	Anti-tack agent

Hypromellose E 5(5cps)	BP/Ph. Eur.	2.48	Binder
Purified Talc	BP/Ph. Eur.	5.11	Lubricant
Ethyl cellulose (10 cps)	USP	0.39	SR Coating Agent
Triacetin	USP-NF	0.04	Plasticizer
Ferric oxide (yellow)	USP-NF	0.09	Colourant
Ferric oxide (red) (PH/IN-919)	USP-NF	0.03	Colourant
Titanium Dioxide	BP/Ph. Eur.	0.35	Opacifier
Methyl alcohol ^	USP	2.21	Solvent
Dichloromethane ^	BP/Ph. Eur.	3.32	Solvent
Purified Water ^	USP/Ph. Eur.	39.27	Solvent
Sub Total 2		**75.00**	
	Total	**165.00**	

Notes for Omeprazole pellets:

1. * Process compensation for API is 2 %
2. # API quantity will vary as per actual Assay & Water Content OR LOD during dispensing of raw material for batch.
3. $ Actual quantity of API dispensed shall be compensated by NPS to match the Standard B. Size.
4. ◆ Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion is 30 % w/w dispersion.
5. ^ Solvents used in the process are evaporated except traces & hence does not appear in batch weight.

Notes for Domperidone pellets:

1. # API quantity will vary as per actual Assay & Water Content OR LOD during dispensing of raw material for batch.
2. $ Actual quantity of API dispensed shall be compensated by NPS to match the Standard B. Size.
3. ^ Solvents used in the process are evaporated except traces & hence does not appear in batch weight.

3. Pharmaceutical Form
Oral Capsules

Description :
A mixture of white to off white & brown to yellowish brown spherical to oval pellets encapsulated in size 3 hard gelatin unprinted capsules with red opaque cap and orange opaque body and strip packed.

4. Clinical Particulars
4.1 Therapeutic Indications
Enteric Coated Omeprazole and Domperidone SR Capsules combines Omeprazole, a proton pump inhibitor, which inhibits the secretion of acid in the stomach and domperidone, a dopamine antagonist which works as an upper gastrointestinal prokinetic agent. It is useful in the treatment of

- Gastroesophageal reflux disease (GERD),
- Dyspepsia caused by gastroparesis and gastroesophageal reflux.

4.2 Posology and method of administration
Adults: The usually recommended dose is one capsule of Enteric Coated Omeprazole and Domperidone SR Capsules once daily before meals.

Elderly: No dosage adjustment is required.

Pediatric use: Safety and efficacy have not been established.

Renal and hepatic impairment: No dosage adjustment is required in patients with renal and hepatic impairment.

4.3 Contraindications
Hypersensitivity to any component of this product.

4.4 Special Warnings and Precautions for Use
Warning
Carefully read the instructions before use.
Do not exceed prescribed dose.
Keep out of reach of children.

Precautions:

In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with Omeprazole, especially on long term use. If a rise in liver enzymes is observed, Enteric Coated Omeprazole and Domperidone SR Capsules should be discontinued. Prior to treatment, malignant disease of the esophagus or stomach should be excluded as the treatment

with Enteric Coated Omeprazole and Domperidone SR Capsules may alleviate the symptoms of malignant diseases and could delay diagnosis.

4.5 Interaction with other medicinal products and other forms of interactions

Omeprazole may reduce or increase the absorption of drugs whose bioavailability is pH dependent (e.g. Ketoconazole).

An interaction of Omeprazole with other drugs which are metabolized by the same enzyme system (Cytochrome P450) cannot be excluded. However no clinically significant interactions were observed in specific tests with a number of such drugs, namely carbamazepine, caffeine, diazepam, Diclofenac, digoxin, ethanol, glibenclamide, metoprolol, nifedipine, phenprocoumon, phenytoin, theophylline, warfarin and an oral contraceptive.

Domperidone may alter the peripheral actions of dopamine agonists such as bromocriptine, including its hypoprolactinaemic action. The actions of domperidone may be antagonised by antimuscarinic and opioid analgesics.

Domperidone may enhance the absorption of concomitantly administered drugs, especially in patients with delayed gastric emptying due of its ability to reduce the gastric emptying time.

4.6 Pregnancy and Lactation

Pregnant women: There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received Omeprazole during pregnancy. Safe use of domperidone in pregnancy has not been established, although studies in animals have not demonstrated teratogenic effects. Therefore, Enteric Coated Omeprazole and Domperidone SR Capsules should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing mothers: Omeprazole and its metabolites are excreted in the milk of rat. It is not known whether Omeprazole is excreted in human milk. Domperidone is excreted in breast milk but at very low levels. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from Omeprazole and because of the potential for tumorigenicity shown for Omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Patients with Renal Impairment & the elderly:

No dosage adjustment is necessary for patient's impairment or for the elderly.

4.7 Effects on Ability to Drive and Use Machines

Not available.

4.8 Undesirable Effects

The components of Enteric Coated Omeprazole and Domperidone SR Capsules, Omeprazole and domperidone, are generally very well tolerated. The reported adverse effects include headache, upper abdominal pain, diarrhoea, constipation, flatulence, eructation, insomnia, hyperglycaemia, pruritus, skin rash, asthenia, back pain, chest pain, neck pain, flu syndrome,infection, migraine, constipation, dyspepsia, gastroenteritis, rectal disorder, vomiting, hyperlipemia, pain, nausea, dizziness, anxiety, hypertonia, bronchitis, increased cough, dyspnoea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, a rise in

serum prolactin which may be associated with galactorrhoea, less frequently with gynaecomastia, breast enlargement or soreness and are rarely observed. There have been rare reports of blurring of vision, peripheral oedema, fever and isolated cases of urticaria, angioedema, depression or myalgia subsiding after termination of therapy, increased liver values and elevated triglyceride levels, acute extrapyramidal dystonic reactions including rare instances of oculogyric crises, occasional rashes, and rare reports of decreased libido and other allergic phenomenon and rare cases of anaphylaxis have also been reported. Inform your doctor in case of any adverse reactions related to drug use.

4.9 Overdose

Capsules if consumed in large quantity may cause confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, flushing, headache, dry mouth, diarrhea, and hyper motility. No specific antidote is known. Omeprazole is extensively protein bound and therefore is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive. Gastric lavage may be useful.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but that suppress gastric acid secretion by specific inhibition of H+/K+ ATPase enzyme system at the secretary surface of the gastric parietal cells. It inhibits the proton pump, which is the final step in the gastric acid secretion

Domperidone is a dopamine antagonist, which works as an upper gastrointestinal prokinetic and increases the tone of the lower esophageal sphincter and enhances gastric emptying. It does not produce dopamine antagonistic effects on central nervous system, probably because it fails to cross the blood brain barrier. It facilitates gastrointestinal smooth muscle activity by inhibiting dopamine at the D1 receptors. Domperidone effectively increases esophageal peristalsis and lower esophageal sphincter pressure (LSEP), increases gastric motility and peristalsis, enhances gastro-duodenal coordination and consequently facilitates gastric emptying.

Domperidone is usually administered before meals as 10 – 20 mg 2 - 3 times a day. Administration of domperidone (30mg) as sustained release pellets enables once daily administration of the drug. This improves the patient compliance without compromising on the efficacy.

5.2 Pharmacokinetic Properties

Omeprazole:

Enteric coated Omeprazole 20 mg and Domperidone SR 30 mg Capsules contain omeprazole as enteric coated pellets (as omeprazole is acid-labile), so the absorption begins only after the pellets leave the stomach. Absorption is rapid with peak plasma levels occurring within 0.5 – 3.5 hours. Peak plasma concentrations of omeprazole & AUC are approximately proportional to doses upto 40 mg. Absolute bioavailability is about 30 – 40% of doses of 20 – 40 mg, due in large part to presystemic metabolism. The plasma half life is 0.5 to 1 hour and the total body clearance is 500 – 600 ml/min. Protein binding is approximately 95%. Following single dose oral administration, little if any unchanged drug is excreted in the urine. The majority of the drug is

eliminated (77%) in urine as at least six metabolites. Two of the metabolites have been identified as hydroxyomeprazole & the corresponding carboxylic acid. The remaining part of the drug is recoverable in the faeces. There is significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in the plasma – sulfide and sulfone derivatives of omeprazole and hydroxyomeprazole. These metabolites have very little or no antisecretary activity.

Domperidone:
Domperidone is absorbed from the gastrointestinal tract and undergoes extensive first passhepatic and gut wall metabolism, which results in an oral bioavailability of 13% to 17%. Total plasma clearance is approximately 700ml/min. The elimination half-life following IV administration is approximately 7.5 hours, while following oral administration half-life is approximately 14 hours. It is secreted in the bile mainly as active metabolites.

5.3 Preclinical safety Data
Preclinical data reveal no special hazard for humans based on conventional studies of general toxicity. Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with Omeprazole or subjected to partial fundectomy. These changes are the result of sustained hypergastrinaemia secondary to acid inhibition. In mutagenicity studies (in-vitro and in-vivo), no findings of clinical relevance did occur for Omeprazole & Domperidone.

6. Pharmaceutical Particulars
6.1 List of Excipients
Non Pareil seeds (18-20#) MgCO3 and HPMC Coated $ (INH) , Hypromellose E 15 BP/Ph. Eur. , Hypromellose E 5 (5cps)BP/Ph. Eur, Purified Talc BP/Ph. Eur , Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion USP , Sodium hydroxide BP/Ph.Eur , Titanium Dioxide BP/Ph. Eur , Glycerol monostearate 40 -50 Ph. Eur., Polysorbate 80 BP/Ph.Eur , Magnesium stearate BP/Ph.Eur , Hypromellose Pthalate (HP 55)BP/Ph.Eur , Dibutyl sebacate USP , Methyl Alcohol USP , Dichloromethane BP/Ph.Eur , Non pareil seeds (18- 20 #) $ INH , Colloidal Anhydrous Silica BP/Ph. Eur. , Ethyl cellulose (10 cps) USP, Triacetin USP -NF , Ferric oxide (yellow) USPNF , Ferric oxide (red) USP-NF ,

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
30 months

6.4 Storage
Keep out of reach of children; Protect form light and moisture; Store below 25°C in a dry place.

6.5 Nature and Contents of Container
Strip pack containing 10 capsules; Carton containing 3 strips of 10 capsules each (3 x 10 capsules).

6.6 Special precautions for disposal and other handling
No special requirements for disposal .

7. Marketing Authorization Holder:

Mega lifesciences Public Company Limited.

8. Marketing Authorization Numbers:
20/1582/DGCS&PHS/2016

9. Date of first authorization / renewal of the authorization:
Date of first authorization: 15-04-2016

10. Date of revision of the text:

11. Dosimetry (If Applicable)
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)
Not Applicable