SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

Delanzo® DDR (Dexlansoprazole) Capsule 30mg

Delanzo® DDR (Dexlansoprazole) Capsule 60mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Delanzo® DDR Capsule 30mg
Each capsule contains:
Dexlansoprazole dual delayed release pellets MS
eq. to Dexlansoprazole.....30mg

Delanzo® DDR Capsule 60mg
Each capsule contains:
Dexlansoprazole dual delayed release pellets MS
eq. to Dexlansoprazole.....60mg

3. PHARMACEUTICAL FORM

Capsule

Appearance:
Delanzo® DDR Capsule 30mg: Grey opaque cap with "Delanzo DDR 30mg" printed on it and blue opaque body with "ﷺ" printed on it 3 times.
Delanzo® DDR Capsule 60mg: Reddish brown cap with "Delanzo DDR 60mg" printed on it and blue opaque body with "ﷺ" printed on it 3 times.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Healing of Erosive Oesophagitis: Delanzo® DDR is indicated for healing of all grades of erosive oesophagitis for up to eight weeks.
Maintenance of Healed Erosive Oesophagitis: Delanzo® DDR is indicated to maintain healing of erosive oesophagitis and relief of heartburn for up to six months.
Symptomatic Non-Erosive Gastroesophageal Reflux Disease: Delanzo® DDR is indicated for the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Delanzo® DDR Dosing Recommendations

Indications	Recommended Dose	Frequency
Healing of Erosive Oesophagitis	60mg	Once daily for up to 8 weeks
Maintenance of Healed Erosive Oesophagitis and relief of heartburn	30mg	Once daily (Controlled studies did not extend beyond 6 months)
Symptomatic NonErosive GERD	30mg	Once daily for 4 weeks

Hepatic Impairment: No adjustment for Delanzo® DDR is necessary for patients with mild hepatic impairment (Child-Pugh Class A). Consider a maximum daily dose of 30mg for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).
Renal impairment: No dosage adjustment is necessary for patients with renal impairment.
Elderly: Due to reduced clearance of dexlansoprazole in the elderly an adjustment of dose may be necessary based on individual requirements. A daily dose of 60mg should not be exceeded in the elderly unless there are compelling clinical indications.
Paediatric population: The safety and efficacy of dexlansoprazole in children and adolescents under 18 years of age have not been established. No data are available.
Important Administration Information:

- Delanzo® DDR can be taken without regard to food.
- Delanzo® DDR should be swallowed whole.
- Delanzo® DDR should not be chewed.

For patients who have difficulty swallowing capsules, follow the instructions below for administration:
Administration with Applesauce:
1. Place one tablespoon of applesauce into a clean container.
2. Open capsule.
3. Sprinkle intact granules on applesauce.
4. Swallow applesauce and granules immediately. Do not chew granules. Do not save the applesauce and granules for later use.

Administration with Water in an Oral Syringe:
1. Open the capsule and empty the granules into a clean container with 20mL of water.
2. Withdraw the entire mixture into a syringe.
3. Gently swirl the syringe in order to keep granules from settling.
4. Administer the mixture immediately into the mouth. Do not save the water and granule mixture for later use.
5. Refill the syringe with 10mL of water, swirl gently, and administer.
6. Refill the syringe again with 10mL of water, swirl gently, and administer.

Administration with Water via a Nasogastric Tube:
1. Open the capsule and empty the granules into a clean container with 20mL of water.
2. Withdraw the entire mixture into a catheter-tip syringe.
3. Swirl the syringe gently in order to keep the granules from settling, and immediately inject the mixture through the nasogastric tube into the stomach. Do not save the water and granule mixture for later use. 4. Refill the syringe with 10mL of water, swirl gently, and flush the tube.
5. Refill the syringe again with 10mL of water, swirl gently, and administer.

4.3. CONTRAINDICATIONS:

Dexlansoprazole is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with dexlansoprazole use. Acute interstitial nephritis has been reported with other proton pump inhibitors (PPIs), including lansoprazole. Dexlansoprazole should not be administered with atazanavir or nelfinavir.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Gastric Malignancy: Symptomatic response with dexlansoprazole does not preclude the presence of gastric malignancy.
Acute Interstitial Nephritis: Acute interstitial nephritis has been observed in patients taking PPIs including lansoprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue dexlansoprazole if acute interstitial nephritis develops.
Cyanocobalamin (vitamin B12) Deficiency: Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.
***Clostridium Difficile* Associated Diarrhoea:** Published observational studies suggest that PPI therapy like dexlansoprazole may be associated with an increased risk of *Clostridium difficile* associated diarrhoea, especially in hospitalized patients. This diagnosis should be considered for diarrhoea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
Bone Fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines.
Hypomagnaesemia: Hypomagnaesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnaesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnaesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.
Concomitant Use of Dexlansoprazole with Methotrexate: Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients.
This medicinal product contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Drugs with pH-Dependent Absorption Kinetics: Due to its effects on gastric acid secretion, dexlansoprazole can reduce the absorption of drugs where gastric pH is an important determinant of their bioavailability. Like with other drugs that decrease the intragastric acidity, the absorption of drugs such as ampicillin esters, ketoconazole, atazanavir, iron salts, erlotinib, and mycophenolate mofetil (MMF) can decrease, while the absorption of drugs such as digoxin can increase during treatment with dexlansoprazole. Dexlansoprazole is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, dexlansoprazole should not be co-administered with atazanavir. Co-administration of PPIs in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to

the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Use dexlansoprazole with caution in transplant patients receiving MMF.
Warfarin: Co-administration of dexlansoprazole 90mg and warfarin 25mg did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with dexlansoprazole and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.
Tacrolimus: Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Clopidogrel: Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of dexlansoprazole.
Methotrexate: Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxy methotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted.

4.6. FERTILITY, PREGNANCY AND LACTATION:
Fertility: There were no adverse foetal effects in animal reproduction studies of dexlansoprazole in rabbits. A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately nine times the maximum recommended human dexlansoprazole dose (60mg/day) revealed no evidence of impaired fertility or harm to the foetus due to dexlansoprazole.
Pregnancy: Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. Because animal reproduction studies are not always predictive of human response, dexlansoprazole should be used during pregnancy only if clearly needed.
Breast-feeding: It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole 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.

4.7. UNDESIRABLE EFFECTS:
The following adverse reactions have been identified during post-approval of dexlansoprazole. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Blood and Lymphatic System Disorders: Autoimmune haemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy.
Ear and Labyrinth Disorders: Deafness, vertigo.
Eye Disorders: Blurred vision, visual disturbance.
Gastrointestinal Disorders: Oral oedema, pancreatitis, diarrhoea, abdominal pain, nausea, abdominal discomfort, flatulence, constipation, vomiting, dry mouth, candidiasis.
General Disorders and Administration Site Conditions: Facial oedema, asthenia, appetite changes.
Hepatobiliary Disorders: Drug-induced hepatitis, abnormal liver function test.
Immune System Disorders: Anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal), anaphylactic reaction, hypersensitivity.
Infections and Infestations: *Clostridium difficile* associated diarrhoea.
Metabolism and Nutrition Disorders: Hypomagnaesemia, hyponatremia.
Musculoskeletal System Disorders: Bone fracture (Hip, wrist or spine).
Nervous System Disorders: Cerebrovascular accident, transient ischemic attack, headache, dizziness, altered taste, convulsions, paraesthesia.
Renal and Urinary Disorders: Acute renal failure.
Respiratory, Thoracic and Mediastinal Disorders: Pharyngeal oedema, throat tightness, cough.
Skin and Subcutaneous Tissue Disorders: Generalized rash, leukocytoclastic vasculitis, urticaria, pruritus.
Psychiatric disorders: Insomnia depression, auditory hallucinations.
Vascular Disorders: Hypertension, hot Flushes.

4.8. OVERDOSE:
Multiple doses of dexlansoprazole 120mg and a single dose of dexlansoprazole 300mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of dexlansoprazole 60mg. Non-serious adverse reactions observed with twice daily doses of dexlansoprazole 60mg include hot flashes, contusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by haemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Proton pump inhibitors, **ATC code:** A02BC06.
Mechanism of action: Dexlansoprazole is a PPI that suppresses gastric acid secretion by specific inhibition of the (H+, K+)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid production.

5.2. PHARMACOKINETICS:
The dual delayed release formulation of **Delanzo® DDR** results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs one to two hours after administration, followed by a second peak within four to five hours. Dexlansoprazole is eliminated with a half-life of approximately one to two hours in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple, once daily doses of dexlansoprazole 30mg or 60mg, although mean AUCt and C_{max} values of dexlansoprazole were slightly higher (less than 10%) on Day 5 than on Day 1.
Absorption: After oral administration of dexlansoprazole 30mg or 60mg to healthy subjects and symptomatic GERD patients, mean C_{max} and AUC values of dexlansoprazole increased approximately dose proportionally. When granules of dexlansoprazole 60mg are mixed with water and dosed via NG tube or orally via syringe, the bioavailability (C_{max} and AUC) of dexlansoprazole was similar to that when dexlansoprazole 60mg was administered as an intact capsule.
Distribution: Plasma protein binding of dexlansoprazole ranged from 96.1% to 98.8% in healthy subjects and was independent of concentration from 0.01 to 20mcg/mL. The apparent volume of distribution (V_z/F) after multiple doses in symptomatic GERD patients was 40.3L.
Metabolism: Dexlansoprazole is extensively metabolized in the liver by oxidation, reduction, and subsequent formation of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the cytochrome P450 (CYP) enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4. CYP2C19 is a polymorphic liver enzyme which exhibits three phenotypes in the metabolism of CYP2C19 substrates; extensive metabolizers (*1/*1), intermediate metabolizers (*1/mutant) and poor metabolizers (mutant/mutant). Dexlansoprazole is the major circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the major plasma metabolites are 5- hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the major plasma metabolite.
Elimination: Following the administration of dexlansoprazole, no unchanged dexlansoprazole is excreted in urine. Following the administration of [^{14}C] dexlansoprazole to six healthy male subjects, approximately 50.7% (standard deviation (SD): 9.0%) of the administered radioactivity was excreted in urine and 47.6% (SD: 7.3%) in the faeces. Apparent clearance (CL/F) in healthy subjects was 11.4 to 11.6L/h, respectively, after five days of 30 or 60mg once daily administration.

5.3. PRECLINICAL SAFETY DATA:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development. Lansoprazole is a racemic mixture of R- and S-enantiomers. Following administration of lansoprazole in humans and animals, the major component circulating in plasma is dexlansoprazole, the R-enantiomer of lansoprazole. Therefore, the carcinogenic potential of dexlansoprazole was assessed using existing lansoprazole studies. Dexlansoprazole was positive in the Ames test and in the in vitro chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the in vivo mouse micronucleus test. A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60mg per day), based on body surface area (BSA), revealed no evidence of harm to the fetus due to dexlansoprazole.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:
Delanzo® DDR Capsule 30mg: ● HPMC Shell
Delanzo® DDR Capsule 60mg: ● HPMC Shell

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Delanzo® DDR Capsule 30mg: Alu/Alu blister, pack size 30's.
Delanzo® DDR Capsule 60mg: Alu/Alu blister, pack size 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
No special requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
Innovator's Specs.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

8. MARKETING AUTHORISATION NUMBER(S)
Delanzo® DDR Capsule 30mg: 089145
Delanzo® DDR Capsule 60mg: 089146

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Delanzo® DDR Capsule 30mg: 31st May, 2018
Delanzo® DDR Capsule 60mg: 31st May, 2018

10. DATE OF REVISION OF THE TEXT

ڈیلینزو® ڈی ڈی آر کیپسول

(ڈیکسلینزوپرازول)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری

سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔