Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT:

Trade Name: INIGAST 40

INN: Esomeprazole Tablets 40 mg

2QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each enteric coated tablet contains: -
Esomeprazole Magnesium Trihydrate Eq. to Esomeprazole USP …….40mg
excipient ……qs.
Excipients with known effect: Lactose

3. PHARMACEUTICAL FORM

Oral Tablet

White, oval shaped biconvex, plain on both side and Enteric coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Esomeprazole gastro-resistant tablets are indicated in adults for:

Gastro-Oesophageal Reflux Disease (GERD)

- treatment of erosive reflux oesophagitis.
- long-term management of patients with healed oesophagitis to prevent relapse.
- symptomatic treatment of gastro-oesophageal reflux disease (GORD).

In combination with an appropriate antibacterial therapeutic regimen for the eradication of*Helicobacter pylori* and

- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

Patients requiring continued NSAID therapy

Healing of gastric ulcers associated with NSAID therapy.

Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Treatment of Zollinger Ellison Syndrome

Esomeprazole gastro-resistant tablets are indicated in adolescents from the age of 12 years for:

Gastroesophageal Reflux Disease (GERD)

- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori

4.2 Posology and method of administration

Posology

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed. For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coat may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested.

Adults and adolescents from the age of 12 years

Gastro-Oesophageal Reflux Disease (GERD)

- treatment of erosive reflux oesophagitis 40 mg once daily for 4 weeks. An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.
- long-term management of patients with healed oesophagitis to prevent relapse 20 mg once daily.
- symptomatic treatment of gastro-oesophageal reflux disease (GORD) 20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. In adults, an on demand regimen taking 20 mg

once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

Adults

In combination with an appropriate antibacterial therapeutic regimen for the eradication of*Helicobacter pylori* and

- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

20 mg Esomeprazole Tablets with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy

Healing of gastric ulcers associated with NSAID therapy:

The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.

Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:

20 mg once daily

Prolonged treatment after IV induced prevention of rebleeding of peptic ulcers.

40 mg once daily for 4 weeks after IV induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

The recommended initial dosage is Esomeprazole Tablets 40 mg twice daily. The dosage should then be individually adjusted and treatment continues as long as clinically indicated.

Based on the clinical data available, the majority of patients can be controlled on doses between 80 and 160 mg Esomeprazole daily. With doses above 80 mg daily, the dose should be divided and given twice-daily.

Children below the age of 12 years

Esomeprazole Tablets should not be used in children younger than 12 years since no data is available.

Impaired renal function

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution.

Impaired hepatic function

Dose adjustment is not required in patients with mild to moderate liver impairment.

For patients with severe liver impairment, a maximum dose of 20 mg Esomeprazole Tablets should not be exceeded.

Elderly

Dose adjustment is not required in the elderly.

4.3 Contraindications

Known hypersensitivity to Esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole should not be used concomitantly with nelfinavir.

4.4 Special warnings and special precautions for use:-

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

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance. Patients on on-demand treatment should be instructed to contact their

physician if their symptoms change in character. When prescribing Esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of Esomeprazole should be considered. When prescribing Esomeprazole for eradication of *Helicobacter pylori* possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.This medicinal product contains sucrose. Patients with rare hereditary problems of fructoseintolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter. Co-administration of Esomeprazole with atazanavir is not recommended. If the combination ofatazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; Esomeprazole 20 mg should not be exceeded.

4.5 Interaction with other medicinal products and other forms of interaction Pharmacokinetic Interactions

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with Esomeprazole might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with Esomeprazole.

Esomeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known.

Increased gastric pH during Esomeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with Esomeprazole and concomitant administration is not recommended. Co-administration of Esomeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax and Cmin). Increasing the atazanavir dose to 400 mg did not compensate for the impact of

Esomeprazole on atazanavir exposure. The co-administration of Esomeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without Esomeprazole 20 mg qd. Co-administration of Esomeprazole (40 mg qd) reduced mean nelfinavir AUC, Cmax and Cmin by 36–39 % and mean AUC, Cmax and Cmin for the pharmacologically active metabolite M8 was reduced by 75-92%. For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant Esomeprazole treatment (40 mg qd). Treatment with Esomeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).

Treatment with Esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with Esomeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

Due to the similar pharmacodynamic effects and pharmacokinetic properties of Esomeprazole and Esomeprazole, concomitant administration with Esomeprazole and atazanavir is not recommended and concomitant administration with Esomeprazole and nelfinavir is contraindicated.

Drugs metabolised by CYP2C19

Esomeprazole inhibits CYP2C19, the major Esomeprazole metabolising enzyme. Thus, when Esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing Esomeprazole for on-demand therapy. Concomitant administration of 30 mg Esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam. Concomitant administration of 40 mg Esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients.

It is recommended to monitor the plasma concentrations of phenytoin when treatment with Esomeprazole is introduced or withdrawn. Esomeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUC by 15% and 41%, respectively.

Concomitant administration of 40 mg Esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few

isolated cases of elevated INR of clinical significance have been reported during concomitant treatment.

Monitoring is recommended when initiating and ending concomitant Esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

In healthy volunteers, concomitant administration of 40 mg Esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination halflife ($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with Esomeprazole.

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Studies evaluating concomitant administration of Esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other drugs on the pharmacokinetics of Esomeprazole

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of Esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to Esomeprazole. Concomitant administration of Esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the Esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased Esomeprazole AUC by 280%. A dose adjustment of Esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

4.6 Fertility,Pregnancy and lactation

For Esomeprazole Tablets, clinical data on exposed pregnancies are insufficient. With the racemic mixture Esomeprazole data on a larger number of exposed pregnancies stemmed from epidemiological studies indicate no malformative nor foetotoxic effects.

Animal studies with Esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct

or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

It is not known whether Esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Esomeprazole Tablets should not be used during breast-feeding.

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

4.7 Effects on ability to drive and use machines

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical trials (and also from postmarketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified. Tabulated list of adverse reactions The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be doserelated. The reactions are classified according to frequency very common >1/10; common >1/100 to 1/1,000 to 1/10,000 to

System Organ Class	**Frequency**	**Undesirable Effect**
Blood and lymphatic system	Rare	Leukopenia, thrombocytopenia disorders
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with

		hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Rare	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very Rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) Skin and subcutaneous tissue disorders
	Not known	Subacute cutaneous lupus erythematosus
Musculoskeletal and	Uncommon	Fracture of the hip, wrist or spine

connective tissue disorder	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported concomitantly.
Reproductive system and administration Etc breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

4.9 Overdose:

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280mg were gastrointestinal symptoms and weakness. Single doses of 80 mg Esomeprazole were uneventful. No specific antidote is known.

Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. 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: Proton Pump Inhibitor

ATC Code: A02B C05.

Esomeprazole is the *S*-isomer of Esomeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of Esomeprazole have similar pharmacodynamic activity.

Site and mechanism of action

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, where it inhibits the enzyme H+K+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with Esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour.

After repeated administration with 20 mg Esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6 – 7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of Esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients.

The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for Esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for Esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Therapeutic effects of acid inhibition

Healing of reflux oesophagitis with Esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with Esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

Other effects related to acid inhibition

During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long-term treatment with Esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur at 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 proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

In two studies with ranitidine as an active comparator, Esomeprazole Tablets showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, Esomeprazole Tablets showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged>60 and/or with previous ulcer), including COX-2 selective NSAIDs.

5.2 Pharmacokinetic properties:

Absorption and distribution

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of Esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg Esomeprazole the corresponding values are 50% and 68%, respectively. The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight.Esomeprazole is 97% plasma protein bound.

Food intake both delays and decreases the absorption of Esomeprazole although this has no significant influence on the effect of Esomeprazole on intragastric acidity.

Metabolism and excretion

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of Esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of Esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of Esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The pharmacokinetics of Esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of Esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC 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 Esomeprazole and/or its sulphone metabolite.

Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of Esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of Esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Special patient populations

Approximately 2.9 ±1.5% of the population lacks a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of Esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg Esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers).

Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of Esomeprazole. The metabolism of Esomeprazole is not significantly changed in elderly subjects (71-80 years of age).

Following a single dose of 40 mg Esomeprazole the mean area under the plasma concentration time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of Esomeprazole.

Impaired organ function

The metabolism of Esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of Esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.
No studies have been performed in patients with decreased renal function.
Since the kidney is responsible for the excretion of the metabolites of Esomeprazole but not for the elimination of the parent compound, the metabolism of Esomeprazole is not expected to be changed in patients with impaired renal function.

Paediatric

Adolescents 12-18 years:

Following repeated dose administration of 20 mg and 40 mg Esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentration (tmax) in 12 to 18 year-olds was similar to that in adults for both Esomeprazole doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose (MCC)
Lactose
Maize Starch
Ethylene Diamine Tetra Acetic Acid (EDTA)
Polyvinyl Pyrrolidone (PVPK-30)
Methylene Dichloride (MDC) or Dichloromethane
Croscarmellose Sodium (CCS)
Aerosil (Colloidal Anhydrous Silica)
Talc Purified
Magnesium Stearate
Sodium Starch Glycolate (SSG)
Hydroxy Propyl Methyl Cellulose (HPMC) 5cps
Polyethylene Glycol (PEG 6000)

Isopropyl Alcohol

HPMC phthalate

Dibutyl phthalate

Titanium Dioxide

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light. Keep out reach of the children.

6.5 Nature and contents of container

3x10 Tablets packed in ALU-ALU blister.

7. MARKETING AUTHORISATION HOLDER

BDA HEALTHCARE PVT. LTD.,

Plot No.: B-1, 2, 3, Near Gov. ITI MIDC, Parseoni – 441105,

Taluka: Parseoni, District: Nagpur, M.S., India**.**

8. MARKETING AUTHORISATION NUMBER(S)

06712/08089/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24.10.2021

10. DATE OF REVISION OF THE TEXT

02.07.2023