NovoTEpH® Capsules
(Esomeprazole)

DESCRIPTION:

NovoTEpH® is an enteric-coated pellet formulation of Esomeprazole magnesium. **NovoTEpH®** (Esomeprazole) is the S-isomer of Omeprazole, which inhibits gastric acid secretion more effectively than omeprazole. Chemically it is bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) trihydrate. **NovoTEpH®** (Esomeprazole) is available for oral administration as:

COMPOSITION:

NovoTEpH® 20mg Capsules:
Each capsule contains:
Enteric coated pellets of Esomeprazole Magnesium Trihydrate MS
equivalent to Esomeprazole ……..... 20mg

NovoTEpH® 40mg Capsules:
Each capsule contains:
Enteric coated pellets of Esomeprazole Magnesium Trihydrate MS
equivalent to Esomeprazole ……..... 40mg

CLINICAL PHARMACOLOGY:

Mechanism of Action:

Esomeprazole works by binding irreversibly to the H+/K+ ATPase in the proton pump. Because the proton pump is the final pathway for secretion of hydrochloric acid by the parietal cells in the stomach, its inhibition dramatically decreases the secretion of hydrochloric acid into the stomach and alters gastric pH

PHARMACOKINETICS:

Absorption:

After oral administration peak plasma levels (Cmax) occur at approximately 1.5 hours (Tmax). The Cmax increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20mg to 40mg. At repeated once-daily dosing with 40mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40mg of Esomeprazole. The AUC is decreased by 43% to 53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals. Food delays and decreases the absorption of esomeprazole, but this does not significantly change its effect on the intra-gastric acidity

Distribution:

Esomeprazole is 97% bound to plasma proteins

Plasma protein binding is constant over the concentration range of 2 to 20 µmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L

Metabolism:

NovoTEpH® Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP 3A4 which forms the sulphone metabolite

Excretion:

The Esomeprazole is approximately 1-1.5 hours. Less than 1% of is excreted in the urine. Approximately 80% of an esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces

SPECIAL POPULATIONS:

Geriatric:

The Cmax values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage based on age is not necessary

Paediatric:

The esomeprazole have not been studied in patients <18 years of age

Gender:

The Cmax values were slightly higher (13%) in females than in males at steady state. Dose based on gender is not necessary

Hepatic Insufficiency:

Patients with mild and moderate hepatic insufficiency, the AUCs were within that could be expected in patients with normal liver function. Patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with function. No dosage is recommended for patients with mild to moderate insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a of 20mg once daily should not be exceeded

Renal Insufficiency:

The Esomeprazole in patients with renal impairment are not expected to be altered relative to volunteers as less than 1% of esomeprazole is excreted unchanged in urine

THERAPEUTIC INDICATIONS:

Esomeprazole is indicated for:

GERD

- Treatment of erosive reflux esophagitis
- Long term management of patients with healed esophagitis to prevent relapse
- Symptomatic treatment of gastroesophageal reflux disease (GERD) without esophagitis

As a triple therapy (Esomeprazole plus amoxicillin and clarithromycin) for the Eradication of Helicobacter pylori

- Healing of duodenal ulcer associated with Helicobacter pylori infection
- Prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers

Note:

Inpatients who failed the therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted

DOSAGE AND ADMINISTRATION:

Esomeprazole capsules should be swallowed as a whole with water and taken at least one hour before meals:

- GERD 20mg or healing of erosive esophagitis 40mg once daily for 4 to 8 weeks
- H. pylori eradication to reduce risk of duodenal ulcer, 40mg once daily for 10 days along with Amoxicillin 1000mg daily for 10 days & Clarithromycin 500mg twice daily for 10 days

For patients with severe hepatic insufficiency (Child Pugh Class C) of 20mg once daily should not be exceeded

ADVERSE REACTIONS:

Generally **NovoTEpH®** is very well tolerated but following side effects (<1%) may occur. Adverse events that were reported as possibly or probably related to Esomeprazole with <1% are listed below by body system

Common: Headache, abdominal pain, diarrhea, flatulence, nausea/vomiting, constipation
Uncommon: Dermatitis, pruritus, urticaria, dizziness, dry mouth
Rare: Hypersensitivity reactions e.g. angioedema, anaphylactic reaction
The following adverse drug reactions have been observed for the recemate omeprazole and may occur with esomeprazole:
Central and peripheral nervous system: paresthesia, somnolence, insomnia, vertigo, reversible mental confusion, agitation, aggression, depression and hallucinations, predominantly in severely ill patients
Endocrine: Gynaecomastia
Gastrointestinal: Stomatitis and gastrointestinal candidiasis
Haematological: Leukopenia, thrombocytopenia, agranulocytosis and pancytopenia
Hepatic: Increased liver enzymes, encephalopathy in patients with pre-existing severe liver disease; hepatitis with or without jaundice, hepatic failure
Skin: Rash, Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), alopecia
Other: Malaise, hypersensitivity reactions e.g. fever, bronchospasm, interstitial nephritis. Increased sweating, peripheral edema, blurred vision, taste disturbance and hyponatremia

CONTRAINDICATIONS
Esomeprazole is contraindicated in patients with known hypersensitivity to any of the formulation or to substituted benzimidazoles

WARNINGS AND PRECAUTIONS:
General:
- In the presence of any alarming symptoms (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 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 since the symptomatic response to therapy with esomeprazole does not preclude the gastric malignancy
- Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with Omeprazole, of which Esomeprazole is an enantiomer
- 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 infection possible drug interactions for other component on the triple therapy should be considered
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltose insufficiency should not take this medicine

Paediatric use:
Safety in patients have not been established
Pregnancy:
There are no adequate and well-controlled studies in women. Esomeprazole should be used during only if clearly needed
Nursing Mothers:
Because esomeprazole is likely to be excreted in milk a decision should be made whether to discontinue or to discontinue the drug, taking into account the importance of the mother due to the potential for serious adverse reactions in nursing infants from esomeprazole
Cutaneous and Systemic Lupus Erythematosus:
Mostly cutaneous; new onset or exacerbation of existing disease; discontinue medicine and refer to specialist for evaluation

DRUG INTERACTIONS:
- 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 due to decreased intragastric acidity during treatment with esomeprazole
- Esomeprazole inhibits CYP2C19, the major esomeprazole metabolizing enzyme. Thus, when esomeprazole is combined with drugs metabolized 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

STABILITY:
See expiry on the pack

PRESENTATIONS:
NovoTEpH® 20mg capsules in a pack of 14's
NovoTEpH® 40mg capsules in a pack of 14's

INSTRUCTIONS:
Do not chew or cruch capsule contents
The capsule should be swallowed whole with water
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

نووٹیف کیپسول
(ایسں اومی پرازول)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
کیپسول چبائے بغیر پانی سے نگل لیں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

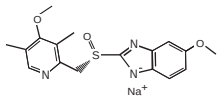
Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

NovoTEpH® Infusion
(Esomeprazole) 40mg

Lyophilized powder for I.V. Injection & Infusion

DESCRIPTION:
NovoTEpH® infusion contains esomeprazole sodium. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S-and R-isomers. Esomeprazole is a proton pump inhibitor and reduces gastric acid secretion

Chemical name:(S)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole sodium
Empirical formula: $C_{17}H_{18}N_3O_3SNa$
Structural formula:



COMPOSITION:
Each vial contains:
Esomeprazole Sodium MS
equivalent to Esomeprazole 40mg
(Suitably buffered)

PHARMACOLOGY:
Mode of Action
Esomeprazole is a proton pump inhibitor 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, esomeprazole blocks the final step in acid production, thus reducing gastric acidity
Pharmacokinetics
Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22L/kg body weight esomeprazole is 97% bound to plasma proteins
Metabolism
Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite
Excretion
Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. Esomeprazole is completely eliminated from plasma and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous esomeprazole is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous esomeprazole
Special Populations:
Hepatic Insufficiency
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing
Geriatric
Dosage adjustment based on age is not necessary
Paediatric
The pharmacokinetics of esomeprazole sodium have not been studied in patients <18 years of age

INDICATIONS:
NovoTEpH® infusion is indicated for gastric anti- secretory treatment when oral route is not possible for short term treatment of GERD patients with a history of erosive esophagitis as an alternative to oral therapy

DOSAGE & ADMINISTRATION:
GERD with a history of Erosive Esophagitis
The recommended adult dose is either 20 or 40mg esomeprazole given once daily by intravenous injection (No less than 3 minutes) or intravenous infusion (10 to 30 minutes)
Hepatic Insufficient Patients
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20mg **NovoTEpH®** infusion should not be exceeded
Elderly
Dose adjustment is not required in the elderly

OR
As directed by the physician

DIRECTIONS FOR RECONSTITUTION AND ADMINISTRATION:
Intravenous injection over no less than 3 minutes
The freeze-dried powder should be reconstituted with 5ml of 0.9% sodium chloride (provided with the pack). Withdraw 5ml of the reconstituted solution and administer as an intravenous injection over no less than 3 minutes

Infusion over 10 to 30 minutes
Dissolve the contents of **NovoTEpH®** vial with 5ml of solvent (0.9% of Sodium Chloride solution for injection, Lactated Ringer's injection or 5% Dextrose injection) and further diluting the resulting solution to a final volume of 100ml. The solution (admixture) should be administered as an intravenous infusion over a period of 10 to 30 minutes

General Information
NovoTEpH® I.V for injection should not be administered concomitantly with any other medications through the same intravenous site and/or tubing. The intravenous line should always be flushed with either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP both prior to and after administration of **NovoTEpH®** I.V for injection
The admixture should be stored at room temperature up to 30°C (86°F) and should be administered within the designated time period as listed in table below. No refrigeration is required

Store time for Final (diluted) Product

Diluent	Administer within:
0.9% Sodium chloride injection, USP	12 hours
Lactated Ringer's injection	12 hours
5% Dextrose injection, USP	6 hours

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

As soon as oral therapy is possible or appropriate, intravenous therapy with **NovoTEpH®** I.V. for injection should be discontinued and the therapy should be continued orally

ADVERSE REACTIONS:
The common adverse reactions reported during therapy of esomeprazole are
Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
The uncommon adverse reactions reported during therapy of esomeprazole are
Peripheral oedema, insomnia, dizziness, paresthesia, somnolence
The rare adverse reactions reported during therapy of esomeprazole are
Leukopenia, thrombocytopenia, hypersensitivity reactions e.g., fever, angioedema and anaphylactic reaction/shock, hyponatremia, agitation, confusion, depression, taste disturbance, bronchospasm, stomatitis, gastrointestinal candidiasis, hepatitis with or without jaundice, alopecia, photosensitivity, arthralgia, myalgia, malaise, increased sweating
The very rare adverse reactions reported during therapy of esomeprazole are
Aggression, hallucinations, hepatic failure, encephalopathy in patients with pre-existing liver disease, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), muscular weakness, interstitial nephritis, gynecomastia

CONTRAINDICATIONS:
- Esomeprazole is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles or to any of the excipients of this medicinal product
- Esomeprazole, like other PPIs, should not be administered with atazanavir

WARNINGS AND PRECAUTIONS:
General
- In the presence of any alarm symptom (e.g., Significant unintentional weight loss, recurring vomiting, dysphagia, hematemesis, or melaena) and when gastric ulcer is suspected to present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis
- Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which esomeprazole is an enantiomer

Hepatic Insufficient Patients
Dose reduction in patients with severe hepatic disease should be considered
Renal Insufficient Patients
Patients with severe renal insufficiency should be treated with caution when administered with esomeprazole injections or infusions
Paediatric Patients
The safety and effectiveness of esomeprazole sodium have not been established for paediatric patients
Pregnancy
Caution should be exercised when prescribing esomeprazole injections and infusions to pregnant women as limited data on exposed pregnancies are available
Nursing mothers
No studies in lactating women have been performed. Therefore, esomeprazole injections and infusions should not be used during breast feeding
Cutaneous and Systemic Lupus Erythematosus
Mostly cutaneous; new onset or exacerbation of existing disease; discontinue medicine and refer to specialist for evaluation

DRUG INTERACTIONS:
- 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. As 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 inhibits CYP2C19, the major esomeprazole metabolizing enzyme. Thus, when esomeprazole is combined with drugs metabolized 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
- Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time

STABILITY:
See expiry on the pack

PRESENTATION:
NovoTEpH® infusion available in a pack of 1 x 40mg (Lyophilized powder) vial + 5ml 0.9% w/v sodium chloride injection

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine
The reconstituted solution should be administered within 12 hrs. after preparation

نووٹیف انفیوژن

(ایسوامی پرازول) ۴۰ ملی گرام

لائیوفلائیزڈ پاوڈر برائے

آئی وی انجکشن/انفیوژن

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com