NOLTEC®

Ilaprazole

Enteric-coated Tablet 10 mg

COMPOSITION

Each enteric-coated tablet contains:

Ilaprazole .....10 mg

DRUG DESCRIPTION

NOLTEC® delayed-release orange color enteric-coated oval tablet with black imprint "Noltec 10" on one side.

PHARMACOLOGY

Mechanism of Action

Ilaprazole belongs to a class of substituted benzimidazole molecules, chemical. A substituted benzimidazole similar to other PPIs, Ilaprazole selectively and irreversibly inhibits the hydrogen/potassium adenosine triphosphatase (H^+-K^+-ATPase) proton pump of the parietal cells in the stomach by forming covalent sulfide bonds with the enzyme at low gastric pH. Ilaprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphydryl group of H^+/K^+ATPase causing inhibition of the enzyme activity. This blocks the final process in H^+ (proton) production, thus reducing gastric-acid secretion.

Pharmacodynamic Properties

Antisecretory Activity

After oral dosing with Ilaprazole 10 mg and 20 mg the onset of effect occurs within one hour. After five days of oral dosing with 10 mg and 20 mg of Ilaprazole, intragastric pH above 4 was maintained for a mean time of 17.6, 19.1 hours and mean intragastric pH over 24 hours was 4.62, 4.89. The proportion of patients maintaining an intragastric pH above 4 for time after dosing; 0-4 hours, >4-9 hours, >9-12 hours, >12-16 hours, >16-24 hours for Ilaprazole 10 mg were 84.8%, 83.7%, 78.7%, 91.7% and 50.1%, respectively. Corresponding proportions for Ilaprazole 20 mg were 85.6%, 92.1%, 87.8%, 97.4% and 57.2%. Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Table 1. Mean Intragastric pH Results on Day 5 (N=40)

	Mean Intragastric pH for Each Dosing Regimen			
	10 mg (A)	20 mg (B)	40 mg (C)	Active Control (D)
Total 24 hours	4.62	4.89***	5.19***	4.50
0-4 hours	4.94	5.01	5.22*	4.91

>4-9 hours	4.84***	5.08	5.35	5.26
>9-12 hours	4.84	5.10	5.37	5.07
>12-16 hours	5.45	5.66*	5.76**	5.37
>16-24 hours	3.84***	4.25***	4.72***	3.17

*,**,*** indicate statistical significance at the 0.05, 0.01, or 0.001 level, respectively (A vs D, B vs D, C vs D).

D = esomeprazole 40mg

Table 2. Percentage of Time Intragastric pH Exceeded 4 on Day 5 (N=40)

	Mean Percentage of Time pH Exceeded 4 for Each Dosing Regimen (%)			
	10 mg (A)	20 mg (B)	40 mg (C)	Active Control (D)
Total 24 hours	73.37	79.70***	85.45***	71.71
0-4 hours	84.77	85.58	90.44**	83.09
>4-9 hours	83.68**	92.06	95.44	92.65
>9-12 hours	78.68	87.75	91.18*	83.58
>12-16 hours	91.73	97.43*	97.06*	89.89
>16-24 hours	50.09**	57.17***	68.75***	39.43

*, **, *** indicate statistical significance at the 0.05, 0.01, or 0.001 level, respectively (A vs D, B vs D, C vs D).

D = esomeprazole 40mg

During the evening and overnight hours (>12 to 16 and >16 to 24 hours), the mean percentage of time intragastric pH exceeded 4 with Ilaprazole 10 mg, 20 mg was higher than any other PPIs.

Therapeutic Effects of Acid Inhibition

A rapid relief of symptoms is obtained by 10-20 mg daily, and most patients with duodenal ulcer recover within 2 weeks, patients with gastric ulcer and reflux esophagitis within 4 weeks.

Healing of erosive esophagitis with Ilaprazole 20 mg occurs in approximately 87% after 8 weeks. Healing of gastric ulcer with Ilaprazole 10 mg occurs in approximately 84% after 6 weeks. Healing of duodenal ulcer with Ilaprazole 10 mg occurs in approximately 92% after 4 weeks.

Pharmacokinetic Properties

Absorption and Distribution

NOLTEC® is an enteric-coated (gastro-resistant) tablet formulation of Ilaprazole as a racemate of two active enantiomers. Ilaprazole is acid-labile. Absorption of Ilaprazole is rapid, with peak plasma levels occurring approximately 3-4 hours after 20 mg dose. Food intake delays the absorption of Ilaprazole although this has no significant influence on the effect of Ilaprazole on intragastric acidity. Over the dose range of 10 to 40 mg, mean AUC and Cmax values for Ilaprazole are increased with increasing doses of Ilaprazole. Ilaprazole exhibits 35% bioavailability with a single dose. The apparent volume of distribution at steady state in healthy subjects is approximately 24.11 L. Ilaprazole is 98.9% plasma protein bound.

The pharmacokinetic profile of Ilaprazole was determined in 30 healthy subjects following repeated once daily administration of 10 mg, 20 mg, 40 mg of Ilaprazole over a period of five days. The results are shown in the following table:

Table 3. Pharmacokinetic Parameters of Ilaprazole on Day 5 Following Oral Dosing for 5 Days

Parameter (CV)	**Ilaprazole 10 mg**	**Ilaprazole 20 mg**	**Ilaprazole 30 mg**
AUC (ng.h/mL)	2092 (27%)	4463 (24%)	7918 (28%)
C_{max} (ng/mL)	293 (34%)	638 (27%)	1114 (27%)
T_{max} (h)	4.5	3.8	3.5
$T_{1/2}$ (h)	5.1	5.2	5.3

Metabolism and Excretion

The harmonic mean for the total Ilaprazole $t_{1/2z}$ following daily administration of Ilaprazole ranged from 5.1 to 5.3 hours and was similar across all doses, and the total body clearance is estimated to be 4.6 to 5.3 L/h.

Ilaprazole was extensively metabolized by oxidation, reduction and conjugation to several metabolites in plasma, urine, and feces. Although Ilaprazole was the major component detected in plasma, Ilaprazole Sulfide and Ilaprazole Sulfone were the major metabolites observed. Ilaprazole was not detected in the urine and feces. Urine consisted of metabolites with the majority glucuronyl or sulfonyl conjugates of Ilaprazole and its metabolites. Fecal consisted of metabolites derived mainly from the conjugation and/or oxidation of Ilaprazole Sulfide.

In vitro studies with human liver microsomes indicated Ilaprazole is metabolised by isoenzymes of CYP450 (Major: CYP2C19 and Minor: CYP3A4). In vivo status these findings indicate that no interaction is expected between Ilaprazole and Midazolam (CYP3A4 substrates).

Following a single 40 mg ^{14}C labelled oral dose of Ilaprazole, 95% of the radioactive dose was recovered in the excreta and with nearly equal distribution between urine and feces.

Special Populations

Gender

Following repeated, once daily administration of Ilaprazole 10 mg for 7 days, mean Ilaprazole Css, max and AUCτ by sex was no significant gender differences in pharmacokinetic parameters after adjusting body weight and no significant difference was shown from a comparison by sex in the effect on gastric acid secretion.

CYP2C19 Polymorphism

Following repeated, once daily administration of Ilaprazole 10 mg for 7 days, mean Ilaprazole Css, max and AUCτ obtained from the Ilaprazole concentration curve by CYP2C19 genotype was no significant difference between CYP2C19 extensive metabolizers and poor metabolizers. CYP2C19 genotype, no significant difference was noted for the effect on gastric acid secretion.

Renal Dysfunction

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of Ilaprazole but not for the elimination of the parent compound, the metabolism of Ilaprazole is not expected to be changed in patients with impaired renal function.

Hepatic Dysfunction

No studies have been performed in patients with decreased hepatic function. Ilaprazole, as is the case with other members of the proton pump inhibitor (PPI) class of compounds, is metabolized through hepatic drug metabolizing system. Patient whose liver function is depressed should use with care.

Elderly

Ilaprazole is mostly metabolized in the liver. Therefore liver function in the elderly is usually depressed. Use it carefully and withdraw it in case of adverse reactions.

INDICATIONS

NOLTEC® is a proton pump inhibitor indicated for the following:

- Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD)
- Treatment of Duodenal Ulcer (DU)
- Treatment of Gastric Ulcer (GU)

CONTRAINDICATIONS

NOLTEC® is contraindicated in patients with known hypersensitivity to any component of the formulation [see **Excipients**] or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, angioedema, bronchospasm, acute interstitial nephritis, and urticaria.

Proton pump inhibitors including **NOLTEC®** should not be administered with Atazanavir or Ritonavir. [see **Drug Interactions**]

Patient who is receiving Rilpivirine-containing products should not be administered with **NOLTEC®**. [see **Drug Interactions**]

ADVERSE REACTIONS

Clinical Trials for Gastric and Duodenal Ulcer

This is safety data from a total of 1,399 subjects in clinical trials compared with Omeprazole for four or six weeks. 790 subjects in these subjects received 5 mg or 10 mg/day with **NOLTEC®**. Most adverse reactions during the trial were mild to moderate and **2% or more adverse reactions were headache (3.7%), diarrhea (2.4 %) and fever (2.3%)**.

Adverse reactions reported from the patients administered with **NOLTEC®** during trials were listed by the body organ system and absolute frequency regardless of the causal relation with **NOLTEC®** and reported adverse reactions are as follows (very frequent, rare, very rare were not shown).

Very frequent (1/10), Commonly (≥1/100, <1/10), Occasionally (≥1/1,000, <1/100), Rare (≥1/10,000,< 1/1,000), Very rare (< 1/10,000), n/a (not predictable).

Table 4. Adverse Reactions of Clinical Trials for Gastric and Duodenal Ulcer

Frequency / **Organ**	**Commonly**	**Occasionary**
Blood and Lymphatic System Disorders	Anaemia	Eosinophilia, Neutrophilia, Prothrombin Time Prolonged, Abnormal of Mean Cell Volume, Leukocytosis, Lymphadenopathy
Gastrointestinal System Disorders	Diarrhea, Abdominal Pain Upper, Gastrinoma	Dyspepsia, Hypergastrinemia, Abdominal Pain, Constipation, Flatulence, Gastritis, Nausea, Vomiting, Abdominal Distension, Colonic Polyp, Epigastric Discomfort, Enterogastritis, Psedodiverticulum, Abdominal Discomfort, Appendicitis, Ascites, Cholecystectomy, Colitis, Diarrhoea Infectious, Duodenitis, Eructation, Gastric Cancer, Gastric Sarcoma, Gastrin Secretion Disorder, Hiatus Hernia, Oral Dryness and Saliva Altered, Oropharyngeal Plague, Uesphageal Haemorrhage
Liver and Biliary System Disorders		Hepatic Cirrhosis, Hepatic Steatosis
Pulmonary and Respiratory System Disorders	Cough, Upper Respiratory Infection, Nasopharyngitis	Nasopharyngeal Pain, Rhinitis, Dyspnea, Bronchial Spasm, Nasal Congestion, Nasal Discomfort, Pneumonia, Pulmonary Tuberculosis, Respiratory Insufficiency, Rhinorrhea, Sinusitis
General Disorders and Administration Site Disorder	Fever	Fatigue, Injection Site Rash, Asthenia, Pain, Pitting Edema, Tenderness.
Infection		Herpes Simplex, Herpes Zoster, Influenza, Sepsis
Imunne System Disorders		Hypersensitivity, Urticaria, Food Allergy
Nervous System Disorders	Headache	Dizziness, Insomnia, Amnesia, Migraine, Somnolence
Renal, Urinary and Reproductive System		Hematuria, Urinary Tract Infection, Dysuria, Proteinuria, Reproductive System Albuminuria,

Disorders		Azotemia, Nephrotic Syndrome, Acute Renal Failure, Dysmenorrhea
Skin and Subcutaneous Tissue Disorders	Hypercholesterolaemia	Cellulitis, Excoriation, Pruritus, Dermatosis, Abnormal Hair, Rash, Skin Laceration, Acute Urticaria, Wound Abscess
Metabolism and Nutrition Disorders	Hypercholesterolaemia	Dyslipidemia Hyperglycemia, Hypertriglycemia, Acidosis, Anorexia, Gout, Hypoalbuminemia, Hyperlipidemia
Musculoskeletal and Connective Tissue System Disorders		Arthritis, Myalgia, Arthralgia, Back Pain, Bone Pain, Gouty Arthritis, Joint Swelling, Acute Osteomyelitis
Eye Disorders		Conjunctivitis, Hordeolum, Periorbital Oedema, Eye Swelling
Sensory System Disorders		Dysgeusia
Cardiovascular System Disorders		Hypertension, Sinus Arrhythmia, Palpitation
Other	AST/ALT Increased	LDL Increased, Chest Discomfort, Flank Pain, Gingiva Pain, Tooth Pain, Chest Pain, Blood Calcitonin Abnormal, Blood Creatinine Increased, Blood Triglyceride Increased, Abnormal Transaminase, Urinary Analysis Abnormal, Xanthoma, Laparotomy

Clinical Trials of Erosive Esophagitis

This is safety data from a total of 1,123 subjects in clinical trials compared with Lansoprazole for erosive esophagitis for eight weeks. 764 subjects in these subjects received 5 mg, 20 mg, or 40 mg/day with Ilaprazole. Most adverse reactions during the trial were mild to moderate and **2% or more adverse reactions were hiatal hernia (3.3 %), headache (2.9%), gastritis (2.7%), and diarrhea (2.6%)**.

Adverse reactions reported from the patients administered with **NOLTEC®** during a trial were listed by the body organ system and absolute frequency regardless of the causal relation with **NOLTEC®** and reported adverse reactions are as follows (very frequent, rare, very rare were not shown in the below table).

Very frequent (≥1/10), Commonly (≥1/100, < 1/10), Occasionally (≥1/1,000, <1/100), Rare (≥1/10,000, < 1/1,000), Very rare (< 1/10,000), n/a (not predictable).

Table 5. Adverse Reactions of Clinical Trials for Erosive Esophagitis

Frequency / Organ	Commonly	Occasionaly
Blood and Lymphatic System Disorders		Anaemia
Gastrointestinal System Disorders	Hiatus Hernia, Gastritis, Diarrhea, Abdominal Distention, Nausea, Abdominal Pain, Erosive Gastritis, Abdominal Pain Upper	Diverticulum, Gastric Ulcer, Constipation, Gastric Polyps, Dyspepsia, Flatulence, Duodenitis, Barrett's Esophagus, Colonic Polyp, Abdominal Tenderness, Impaired Gastric Emptying, Vomiling, Toothache, Erosive Hiatus Hernia, Gastritis, Duodenitis, Abdominal Pain Lower, Urgency Defaecation, Rectal Diarrhea, Abdominal Hemorrhage, Hematochezia, Abdominal Discomfort, Gastrointestinal Sounds Abnormal, Abnormal Faeces, Faecal Volume Increased, Faecal Discolored, Faeces Hard, Mallory-Weiss Syndrome, Gastroesophageal Reflux Disease, Enteritis, Gastric Mucosal Lesion, Esophageal Dysplasia, Stomach Discomfort, Lower Gastrointestinal Haemorrhage, Esophageal Disorder, Acquired Esophageal Web, Erosive Esophagitis, Ascites, Proctitis, Dry Mouth, Lip Dry
Respiratory, Thoracic and Mediastinal Disorders		Cough, Dyspnea, Nasal Congestion, Throat Irritation, Asthma, Rhonchi, Seasonal Rhinitis, Epistaxis, Pharyngeal Polyp, Respiratory Tract Congestion, Sneezing, Allergic Rhinitis
General Disorders and Administration Site Disorders		Fatigue, Nodule, Irritability, Vessel Puncture Site Haematoma, Infusion Site Pain, Infusion Site Phlebitis, Infusion Site Reaction, Pain, Pyrexia, Chest Discomfort, Early Satiety, Local Swelling, Infusion Site Extravasation, Infusion Site Swelling, Infusion Site Thrombosis, Mucosal Hyperemia, Peripheral Edema, Chest Pain
Infection and Infestations	Upper Respiratory Infection, Nasopharyngitis	Bronchitis, Sinusitis, Influenza, Hordeolum, Viral Pharyngitis, Diverticulitis, Gastroenteritis, Cellulitis, Folliculitis, Esophageal Candidiasis,

	Urinary Tract Infections	Chlamydial Infection, Tooth Abscess, Tooth Infection, Ear Infection, External Otitis, Otitisinterna, Onychomycosis, Vulvovaginal Mycotic Infection, Helicobacter Gastritis, Helicobacter Infection, Abscess, Groin Abscess, Stitch Abscess, Wound Infection, Pneumonia, Prostate Infection, Staphylococcal Skin Infection, Treptococcal Pharyngitis, Acute Sinusitis, Chronic Tonsillitis, Peritonsillar Abscess, Pharyngitis, Viral Gastroenteritis, Viral Infection, Viral Rhinitis, Herpes Simplex, Rhinitis
Immune System Disorders		Seasonal Allergy, Allergy To Arthropod Bite
Nervous System Disorders	Headache	Dizziness, Migraine, Anxiety, Depression, Insomnia, Syncope, Hypogeusia, Bipolar Disorder, Suicide Attempt, VII Nerve Paralysis
Renal, Urinary and Reproductive System Disorders		Hematuria, Pollakiuria, Renal Cyst, Proteinuria
Skin and Subcutaneous Tissue Disorders		Rash, Pruritus, Dry Skin, Contact Dermatitis, Onycholysis, Papular Rash, Subcutaneous Rash Pruritus, Rosacea
Metabolism and Nutrition Disorders		Anorexia, Hyperglycaemia, Dehydration, Diabetic Ketoacidosis, Hypercholesterolaemia, Hyperkalaemia, Hypokalemia, Diabetic Mellitus
Musculoskeletal and Connective Tissue Disorders		Back Pain, Arthralgia, Pain In Extremity, Muscle Spasms, Myalgia, Tendonitis, Intervertebral Disc Protrusion, Joint Crepitation, Musculoskeletal Pain, Rheumatoid Arthritis, Tendon Calcification, Neck Pain, Flank Pain, Lymphoma, Vulvovaginal Papilloma
Eye Disorders		Eye Swelling
Ear and Labyrinth Disorders		Ear Pain, Cerumen Impaction, Deafness, Tinnitus
Cardiac System Disorders		Left Ventricle Bundle Branch Block, Palpitations, Tachycardia, Atrial Fibrillation, Sinus Arrhythmia,

		Sinus Bradycardia, Ventricular Disorders Extrasystole
Endocrine System Disorders		Hypothyroidism
Injury, Poisoning and Procedural Complications		Procedural Nausea, Contusion, Joint Sprain, Limb Injury, Post Procedural Complication, Post Procedural Discomfort, Skin Laceration, Respiratory Fume Inhalation Disorder, Medical Device Related Complications, Procedural Vomiting, Meniscus Lesion, Tibia Fracture, Muscle Sprain, Procedural Dizziness, Arthropod Bite, Excoriation, Fall, Procedural Pain, Accidental Overdose, Intentional Overdose, Sunburn, Scratch, Rib Fracture
Investigations	Alanine Aminotransferase Increased	Blood Gastrin Increased, Liver Function Test Abnormal, White Blood Cells Urine Positive, Aspartate Aminotransferase Increased, Hepatic Enzyme Increased, Haematocrit Increased, Weight Increased, Blood Alkaline Phosphatase Increased, Bacteria Urine Identified, Helicobacter Pylori Identification Test Positive, Blood Glucose Increased,Electrocardiogram QT Prolonged, Electrocardiogram T Wave Abnormality, Transaminase Increased, Blood Uric Acid Increased, Haemoglobin Decreased, Mean Red Blood Cell Volume Decreased, Red Blood Cell Count Decreased, Blood Creatinine Decreased, Protein Urine Present, Blood Pressure Increased, Blood Triglycerides Increased, White Blood Cell Count Increased
Vascular Disorders		Hypertension, Hot Flush
Reproductive System and Breast Disorders		Breast Pain, Spontaneous Abortion

Adverse Reactions in Post-Marketing Surveillance (PMS)

Infections

Unknown frequency: *Clostridium difficile*-associated diarrhea.

Metabolism and Nutrition

Unknown frequency: Hypomagnesemia.

Blood and Lymphatic System

It was reported that Proton Pump Inhibitors might be related to agranulocytosis and pancytopenia.

Followings are Reported Adverse Reactions According to Post-Marketing Surveillance of PPI

Since these adverse reactions are reported spontaneously from an unspecified large number of population group, they are not always possible to reliably predict the incidence or to establish a causal relationship with administration.

Immune System

Unknown frequency: Systemic lupus erythematosus.

Skin and Subcutaneous Tissue

Unknown frequency: Cutaneous lupus erythematosus.

Post-Marketing Surveillance (PMS)

From a post-marketing surveillance (PMS) that was conducted over 6 years which involved 7,617 patients for Korean re-examination, the adverse event (AE) incidence was reported as 0.29 % (22/7,617 patients, 23 events in total), irrespective of the causal relationship. No single serious adverse event (SAE) was reported. The incidence of unexpected AEs was reported as 0.01% (1/7,617 patients, 1 event in total), irrespective of the causal relationship, and the event was heartburn at 0.01% (1/7,617 patients, 1 event in. total). Of these, the incidence of unexpected AEs for which could not be exclusive to the causal relationship with Ilaprazole was 0.01 % (1/7,617 patients, 1 event in total), and such an event was **heartburn** at 0.01% (1/7,617 patients, 1 event in total).

AFs of Ilaprazole from the PMS for Korean re-examination and the spontaneous adverse event reports were comprehensively evaluated at the end of the re-examination period by comparing with AE reports for all other drugs approved for marketing in Korea. For the result of evaluation, AE of Ilaprazole has no statistically significant difference in the AEs rate compared to AEs of all other drugs.

WARNINGS AND PRECAUTIONS

Gastric Malignant Tumor

The symptoms of a malignant tumor could be relieved or a diagnosis could be delayed due to **NOLTEC®**, so patients should be screened to identify a malignant tumor in case of gastric ulcer with premonitory symptoms (unintended remarkable weight loss, recurrent vomit, dysphagia, hematemesis or black vomit) of a malignant tumor. X-ray or endoscopy is used in the early stage in case of possible tumor of stomach. If it is confirmed as gastric cancer, stop using **NOLTEC®**.

***Clostridium Difficile* Associated Diarrhea**

Decreased gastric acidity due to PPI might be expected to increase gastric counts of bacteria normally presented in the gastrointestinal tract. Treatment with **NOLTEC®** may lead to a slightly increased risk of

gastrointestinal infections such as *Salmonella*, *Campylobacter* and *Clostridium difficile*. Published observational studies suggest that PPIs may be associated with increased risk of diarrhea related to *Clostridium difficile*, especially in hospitalized patients. This diagnosis should be considered when the diarrhea has not been improved. [see **Adverse Reactions**]. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture

It was reported that proton pump inhibitors might be related to increasing the risk of hip joint, wrist and spine fracture in some epidemiologic studies. The risk of fracture increased in the patients who received a high dose exceeding recommendations and who used PPI in the long term more than 1 year. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of Vitamin D and Calcium.

Hypomagnesemia

In patients treated with Proton Pump Inhibitors more than three months, hypomagnesemia was rarely reported and it was the most frequent in case of treatment more than 1 year. Most patients need to supplement magnesium and stop using Proton Pump Inhibitors to treat hypomagnesemia. Regular magnesium monitoring is necessary from the beginning of treatment for the patients who need longterm treatment, or combine digoxin or hypomagnesemia inducing drugs (e.g. diuretics). Serious adverse reactions include rigidity, arrhythmia and seizure. [see **Adverse Reactions**]

Hepatic or Renal Dysfunction

NOLTEC® should be used with caution in patients with hepatic or renal dysfunction. [see **Use In Specific Populations**]

Malabsorption of Vitamin B12

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 B-12) caused by hypo-or achlorhydria.

Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE. The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement. Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported. Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving **NOLTEC®**, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation

of the PPI alone in 4 to 12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations. [see **Adverse Reactions**]

Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop **NOLTEC®** treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Use in Spesific Populations

Pregnancy

Pregnancy Category B

The clinical relevance of these findings is unknown. Because animal reproduction studies are not always predictive of human response. **NOLTEC®** is treated only when the therapeutic benefit exceeds the risk to pregnant women or possibly pregnant women.

In the result of rat fertility test and early embryogenesis test, maternal NOAEL was 320 mg/kg/day and fetus in 320 mg/kg/day group showed malformation of internal organs and osteodystrophy. Embryo-fetus toxicity test was conducted in rats and rabbits. In rat, maternal toxicity and fetus toxicity were not observed. In rabbit, the death of embryo increased, the survived fetus number and the weight of fetus decreased in a dose of 80, 240 mg/kg/day, and ossification delay was observed in fetus in 240 mg/kg/day group. In the result of development test before and after birth and maternal function test in rats, toxicity was observed in a parent (F0) and the next generation (F1) in dosing 200 mg/kg/day. The corpus luteum number, implantation number and a litter size decreased in the next generation in dosing 1,000 mg/kg/day.

Nursing Mothers

In the animal study, transition to the milk was reported and the body and liver weight of babies were decreased before and after birth when it is orally administered. Therefore, **NOLTEC®** is not used in lactating women.

Paediatric Use

The use of **NOLTEC®** is not recommended in adolescents below the age of 19 years old as clinical data are limited.

Effects on ability to drive and use machines

Adverse reactions such as Dizziness, Insomnia, Amnesia, Migraine and Somnolence may occur [see **Adverse Reactions**]. Under these conditions the ability to react may be decreased. While taking **NOLTEC®**, do not drive or operate any tools or machines.

Others

Long-term experiences for duodenal ulcer and gastric ulcer were not provided (administration up to for four weeks for duodenal ulcer and six weeks for gastric ulcer), so it is not recommended to use in maintenance

therapy. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

DRUG INTERACTIONS

Antiretroviral Therapy

Concomitant use of Atazanavir or Ritonavir with proton pump inhibitors is not recommended. Coadministration of Atazanavir or Ritonavir with proton pump inhibitors is expected to substantially decrease Atazanavir or Ritonavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance.

Drugs for which Gastric pH can affect Bioavailability

In case of drugs (Ketoconazole, Iron salt, Ampicillin ester) which bioavailability is mostly decided by pH of gastric acid, absorption of a drug might be theoretically inhibited due to a long-term inhibitory action of gastric acid secretion by **NOLTEC®**. Absorption of Ketoconazole and Itraconazole might be reduced during administration of **NOLTEC®**, same as other acid secretion inhibitors or gastric antacids.

Drugs Metabolized through Cytochrome P450

NOLTEC® is metabolized through cytochrome P450, especially by CYP3A4, in the liver, same as other proton pump inhibitors. Interaction could be occurred when combining with drugs metabolized through cytochrome P450, such as cyclosporine, Disulfiram, Benzodiazepines. Patients must be monitored carefully under combination of those drugs and a dose of the drugs is modified, if needed.

Tacrolimus

If Omeprazole, one of family series drugs with Ilaprazole, was combined with Tacrolimus, serum tacrolimus might increase. Serum Tacrolimus is monitored when starting or terminating administration of **NOLTEC®**.

Methotrexate

Case reports and published population pharmacokinetic studies suggest that concomitant use of (primarily at high dose: see Methotrexate prescribing information) some PPIs may elevate and prolong serum levels of Methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to Methotrexate toxicities. However, no formal drug interaction studies of Methotrexate with PPIs have been conducted. In high-dose Methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

Rilpivirine

Do not take **NOLTEC®** with Rilpivirine because when **NOLTEC®** is combined with Rilpivirine, the plasma concentration of Rilpivirine may be decrease (Increased gastric pH). This may reduce the therapeutic effect of Rilpivirine.

DOSAGE AND ADMINISTRATIONS

NOLTEC® is supplied as enteric-coated tablets for oral administration. The recommended dosages are outlined in the table below. The duration of proton pump inhibitor administration should be based on available safety and efficacy data specific to the defined indication and dosing frequency, as described in the Prescribing Information, and individual patient medical needs. Proton pump inhibitor treatment should only

be initiated and continued if the benefits outweigh the risks of treatment. **NOLTEC®** tablets should be taken at least 1 hour before meals and caution patients that **NOLTEC®** enteric-coated tablet should not be split, crushed, or chewed.

Table 5. Recommended Dosage Schedule of **NOLTEC®**

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD) Short-Term Treatment of Erosive Esophagitis	Adults: 20 mg	Once daily for up to 8 weeks
Duodenal Ulcers Short-Term Treatment	Adults: 10 mg	Once daily for up to 4 weeks
Gastric Ulcers Short-Term Treatment	Adults: 10 mg	Once daily for 4 to 6 weeks

Special Populations

Impaired Hepatic or Renal Function

There is no need for a dose adjustment in patients with impaired renal function.

NOLTEC® is mostly metabolized in the liver. Use it carefully and withdraw it in case of adverse reactions with impaired liver function patients. [See **Pharmacology, Pharmacokinetics**]

Elderly

NOLTEC® is mostly metabolized in the liver. Therefore liver function in the elderly is usually depressed. Use it carefully and withdraw it in case of adverse reactions. [See **Special Populations**]

Paediatric Population

The use of **NOLTEC®** is not recommended in adolescents below the age of 19 years old as clinical data are limited.

OVERDOSAGE

Overdose symptoms in human have not been reported yet. Special detoxicants are unknown. Ilaprazole is not dialyzed due to high protein binding ratio (98.9%). Therefore, symptomatic treatment and supportive therapy to be used during overdose.

PATIENT COUNSELLING INFORMATION

- **NOLTEC®** tablets should be taken at least 1 hour before meals and caution patients that **NOLTEC®** enteric-coated tablet should not be split, crushed, or chewed.
- Let patients know that concomitant administration of Antacids does not affect the absorption of **NOLTEC®** enteric-coated tablet.
- Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea. [see **Warnings and Precautions**]

- Advise patients to immediately report and seek care for any cardiovascular or neurological symptoms including rigidity, arrhythmia and seizure as these may be signs of hypomagnesemia. [see **Warnings and Precautions**]

ON MEDICAL PRESCRIPTION ONLY

PRESENTATION

Box, 1 bottle @ 28 enteric-coated tablets

Reg. No. :DKI

EXCIPIENTS

Magnesium Hydroxide, Pregelatinized Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Silicon Dioxide, Talc, Magnesium Stearat, Opadry 03K19229, Acryl-Eze 93F19255, and Opadry 85G630015, Purified Water, Ethanol.

STORAGE

Do not store above 25°C.

Keep the container tightly closed in order to protect from moisture.

Keep out of the reach of children.

SHELF LIFE

3 years.

Manufactured by:

IL-YANG BIOPHARM, CO., LTD

Jecheon-si - Republic of Korea

Imported and distributed by:

PT SANBE FARMA

Cimahi - Indonesia

Brosur Kemasan: Informasi Bagi Pengguna

NOLTEC® Tablet Salut Enterik 10 mg
Ilaprazole

Baca seluruh again brosur ini dengan cermat sebelum Anda mulai meminum obat ini.
- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini mungkin dapat membahayakan mereka, sekali pun gejala-gejala penyakit mereka sama dengan Anda.
- Jika salah satu efek samping menjadi serius, atau jika Anda melihat ada efek samping yang tidak tercantum dalam brosur ini, harap beri tahu dokter atau apoteker Anda

Isi brosur ini:

1. Apa itu NOLTEC® dan apa kegunaannya
NOLTEC® tablet salut enterik mengandung zat aktif Ilaprazole. Ini termasuk dalam kelompok obat yang disebut "penghambat pompa proton". Obat ini bekerja dengan mengurangi jumlah asam yang diproduksi lambung Anda.
NOLTEC® tablet salut enterik digunakan untuk mengobati kondisi berikut:
- Pengobatan esofagitis erosif terkait dengan penyakit refluks gastroesofageal (GERD).
- Pengobatan ulkus duodenum (usus 12 jari).
- Pengobatan ulkus lambung.

2. Apa yang perlu Anda ketahui sebelum meminum NOLTEC®
Jangan meminum NOLTEC® jika:
- Anda alergi (hipersensitif) terhadap Ilaprazole atau bahan lain dari obat ini (tercantum di Bagian 6: Informasi lebih lanjut).
- Anda alergi terhadap obat penghambat pompa proton lainnya (misalnya Pantoprazole, Lansoprazole, Rabeprazole, Omeprazole, Esomeprazole).
- Anda sedang menggunakan obat yang mengandung Atazanavir (digunakan untuk mengobati HIV).
- Anda sedang hamil atau mengira Anda sedang hamil.
- Anda sedang menyusui.
- Anda sedang menggunakan produk yang mengandung Rilpivirine.

Jangan gunakan **NOLTEC®** jika salah satu hal di atas berlaku untuk Anda. Jika Anda tidak yakin, bicarakan dengan dokter Anda atau apoteker sebelum menggunakan obat ini.

Peringatan dan Perhatian

Tanyakan kepada dokter atau apoteker Anda sebelum mengonsumsi **NOLTEC®** jika:
- Anda menderita tumor perut.
- Anda pernah mengalami masalah hati atau ginjal.
- Anda menderita osteoporosis.
- Anda harus menjalani tes darah tertentu (Chromogranin A).

NOLTEC® mungkin menyembunyikan gejala penyakit lain. Oleh karena itu, jika salah satu hal berikut terjadi pada Anda sebelum Anda mulai mengonsumsi obat ini atau saat Anda meminumnya, segera bicarakan dengan dokter Anda:
- Berat badan Anda turun banyak tanpa alasan dan mengalami masalah menelan.
- Anda mengalami sakit perut atau gangguan pencernaan.
- Anda mulai muntah makanan atau darah.
- Anda buang air besar berwarna hitam (kotoran berlumuran darah).

Jika Anda mengalami diare parah (berair atau berdarah) dengan gejala seperti demam, sakit perut atau nyeri tekan, hentikan penggunaan **NOLTEC®** dan segera temui dokter.

Mengonsumsi penghambat pompa proton seperti **NOLTEC®**, terutama dalam jangka waktu lebih dari satu tahun, mungkin sedikit meningkatkan risiko patah tulang di pinggul, pergelangan tangan, atau tulang belakang. Beri tahu dokter Anda jika Anda menderita osteoporosis atau jika Anda sedang mengonsumsi kortikosteroid (yang dapat meningkatkan risiko osteoporosis).

Perawatan harian dengan obat penekan asam apa pun dalam jangka waktu lama (misalnya lebih dari 3 tahun) dapat menyebabkan malabsorpsi Sianokobalamin (vitamin B-12) yang disebabkan oleh hipo-atau aklorhidria.

NOLTEC® tidak boleh digunakan pada anak-anak di bawah usia 19 tahun.

Mengonsumsi obat lain
Anda harus selalu memberi tahu dokter Anda tentang obat apa pun yang Anda pakai. Ini termasuk obat-obatan apa pun yang Anda beli sendiri, serta obat-obatan yang diresepkan oleh dokter untuk Anda. Beberapa obat mungkin berinteraksi dengan **NOLTEC®** tablet salut enterik. Ini termasuk:
- Atazanavir (digunakan untuk mengobati HIV).
- Ketoconazole, Itraconazole (digunakan untuk mengobati infeksi yang disebabkan oleh jamur).
- Carbamazepine (obat Benzodiazepin yang digunakan dalam pengobatan epilepsi).
- Tacrolimus (transplantasi organ).
- Methotrexate (obat kemoterapi yang digunakan dalam dosis tinggi untuk mengobati kanker).
- Rilpivirine (digunakan untuk mengobati HIV).

Kehamilan dan menyusui
- Jangan gunakan **NOLTEC®** jika Anda sedang hamil atau mengira Anda mungkin hamil.
- Jangan gunakan **NOLTEC®** jika Anda sedang menyusui atau berencana untuk menyusui.

Tanyakan kepada dokter atau apoteker Anda untuk nasihat sebelum meminum obat apa pun selama kehamilan atau saat menyusui.

Mengemudi dan menjalankan mesin
Anda mungkin merasa mengantuk saat mengonsumsi **NOLTEC®**, jangan mengemudi atau mengoperasikan alat atau mesin apapun.

3. Cara meminum NOLTEC®

Selalu gunakan **NOLTEC®** persis seperti yang diperintahkan dokter Anda. Anda sebaiknya memeriksakan diri ke dokter atau apoteker jika Anda tidak yakin.

Cara minum obat ini
- Hanya keluarkan tablet dari wadah aslinya atau blister ketika sudah waktunya minum obat.
- Telan tablet Anda utuh dengan segelas air. Jangan mengunyah atau menghancurkan tablet.
- Dokter Anda akan memberi tahu Anda berapa banyak tablet yang harus diminum dan berapa lama penggunaannya. Ini tergantung pada kondisi Anda.
- Jika Anda meminum obat ini untuk waktu yang lama, dokter Anda akan memantau Anda.

Dewasa
- **Pengobatan esofagitis erosif terkait dengan penyakit refluks gastroesofageal (GERD)**
  Dosis umum: dua tablet **NOLTEC®** 10 mg sekali sehari dengan durasi pengobatan hingga 8 minggu.
  Minum tablet di pagi hari sebelum makan.
- **Pengobatan ulkus lambung**
  Dosis umum: satu tablet **NOLTEC®** 10 mg sekali sehari dengan durasi pengobatan selama 4 sampai 6 minggu.
  Minum tablet di pagi hari sebelum makan.
- **Pengobatan ulkus usus (usus 12 jari)**
  Dosis umum: satu tablet **NOLTEC®** 10 mg sekali sehari dengan durasi pengobatan hingga 4 minggu.
  Minum tablet di pagi hari sebelum makan.

Anak-anak
NOLTEC® tidak boleh digunakan pada anak-anak di bawah usia 19 tahun.

Pasien dengan gangguan hati
Dokter Anda akan meresepkan dosis yang lebih rendah dan meningkatkannya jika perlu.

Jika Anda lupa meminum obat ini
Jangan meminum dosis ganda untuk mengganti dosis yang terlupakan. Jika Anda lupa meminum satu dosis, minumlah segera setelah Anda mengingatnya, lalu minum dosis berikutnya pada waktu yang tepat.

Jika Anda mengambil lebih dari yang seharusnya

Jika Anda (atau orang lain) menelan banyak tablet pada saat yang bersamaan, atau Anda merasa seorang anak mungkin telah menelannya, hubungi unit gawat darurat rumah sakit terdekat atau segera beri tahu dokter Anda.
Ambil brosur ini dan sisa tablet yang harus Anda tunjukkan kepada dokter.

4. Kemungkinan efek samping

Seperti semua obat-obatan, **NOLTEC®** tablet salut enterik dapat menyebabkan efek samping pada beberapa pasien. Efek ini biasanya tidak bertahan lama dengan Ilaprazole tetapi Anda harus menemui dokter jika salah satu efek sampingnya parah atau mengganggu Anda.

Khususnya, jika hal-hal berikut ini terjadi, hentikan penggunaan obat Anda dan segera beri tahu dokter Anda atau langsung pergi ke unit gawat darurat di rumah sakit terdekat:

- Sesak napas, wajah bengkak, demam, urtikaria, atau gejala lain dari reaksi alergi serius.
- Kemerahan pada kulit yang melepuh atau mengelupas. Mungkin juga timbul lepuh parah dan pendarahan di bibir, mata, mulut, hidung, dan alat kelamin. Ini bisa jadi merupakan 'sindrom Stevens-Johnson' atau 'nekrolisis epidermal toksik'.
- Kulit kuning, urine berwarna gelap dan rasa lelah yang bisa menjadi gejala masalah liver.

Meskipun ini adalah efek samping serius yang memerlukan perhatian medis segera, namun sangat jarang terjadi.

Umum (mempengaruhi kurang dari 1 dari 10 orang)

- Sakit kepala, demam.
- Diare, sakit perut bagian atas, gastrinoma, perut kembung, sakit perut, mual, hernia hiatus, gastritis.
- Batuk, nasofaringitis, infeksi saluran pernapasan atas.
- Hiperkolesterolemia, ASt/ALT meningkat, anemia.
- Infeksi saluran kemih.

Jarang (mempengaruhi kurang dari 1 dari 100 orang)

- Masalah darah seperti berkurangnya jumlah sel darah putih atau sel darah merah. Hal ini dapat menyebabkan kelemahan, memar, atau membuat infeksi lebih mungkin terjadi.
- Dispepsia, hipergastrinemia, sembelit, perut kembung, muntah, enterogastritis, pseudodivertikulum, radang usus buntu, asites, kolesistektomi, kolitis, diare menular, eruktasi, gangguan sekresi gastrin, kekeringan mulut dan perubahan air liur, bibir kering, gangguan pengosongan lambung, muntah, proktitis, mulut kering, kotoran tidak normal (urgensi, volume meningkat, berubah warna, keras).
- Sirosis hati, steatosis hati.
- Kelelahan, nyeri, pireksia, nyeri dada, edema perifer, asthenia, nyeri tekan.
- Herpes simpleks, herpes zoster, sepsis, kandidiasis esofagus, infeksi klamidia, abses gigi, infeksi gigi, infeksi mikotik vulvovaginal, faringitis streptokokus, sinusitis akut, tonsilitis kronis, abses peritonsillar.
- Pusing, insomnia, amnesia, migrain, somnolen, kecemasan, depresi, sinkop, hipogusia, gangguan bipolar, percobaan bunuh diri, kelumpuhan saraf VII.
- Hematuria, pollakiuria, kista ginjal, proteinuria, hematuria, disuria, albuminuria, azotemia, sindrom nefrotik, gagal ginjal akut.

- Dislipidemia, hiperglikemia, hipertriglikemia, asidosis, anoreksia, asam urat, hipoalbuminemia, dehidrasi, hiperkalemia, hipokalemia, diabetes melitus.
- Sakit punggung, arthralgia, radang sendi, kejang otot, mialgia, sakit leher, sakit pinggang, sakit tulang, pembengkakan sendi.
- Mata bengkak, konjungtivitis.
- Nyeri payudara, aborsi spontan, dismenore.

Frekuensi tidak diketahui
- Diare terkait *Clostridium difficile*.
- Hipomagnesemia.
- Agranulositosis, pansitopenia.
- Lupus eritematosus sistemik.
- Lupus eritematosus kulit.

Jika Anda menggunakan **NOLTEC®** selama lebih dari tiga bulan, ada kemungkinan kadar magnesium dalam darah Anda turun. Kadar magnesium yang rendah dapat dilihat sebagai kelelahan, kontraksi otot yang tidak disengaja, disorientasi, kejang, pusing, peningkatan detak jantung. Jika Anda mengalami gejala-gejala ini, segera beri tahu dokter Anda. Kadar magnesium yang rendah juga dapat menyebabkan penurunan kadar kalium atau kalsium dalam darah. Dokter Anda mungkin memutuskan untuk melakukan tes darah rutin untuk memantau kondisi kadar magnesium Anda.

Jangan khawatir dengan daftar kemungkinan efek samping ini. Anda mungkin tidak mendapatkan satupun dari mereka. Jika salah satu efek samping menjadi serius, atau jika Anda melihat ada efek samping yang tidak tercantum dalam brosur ini, harap beri tahu dokter atau apoteker Anda.

5. Cara menyimpan NOLTEC®
- Jangan simpan di atas 25°C. Simpan dalam kemasan aslinya, untuk melindungi dari kelembapan.
- Jauhkan dari jangkauan dan pandangan anak-anak.
- Jangan gunakan **NOLTEC®** setelah tanggal kadaluarsa yang tertera pada label/karton/botol.
- Obat-obatan tidak boleh dibuang melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat-obatan yang tidak diperlukan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.
- Umur simpan: 3 tahun.

6. Informasi Lebih Lanjut
Apa kandungan NOLTEC®

Setiap **NOLTEC®** 10 mg tablet salut enterik mengandung 10 mg zat aktif Ilaprazole.

Bahan lain yang dikandungnya:

Magnesium Hydroxide, Pregelatinized Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Silicon Dioxide, Talc, Magnesium Stearat, Opadry 03K19229, Acryl-Eze 93F19255, and Opadry 85G630015, Purified Water, Ethanol.

Seperti apa bentuk NOLTEC® dan isi kemasannya

- **NOLTEC®** 10 mg tablet salut enterik berbentuk oval dan berwarna oranye.
- Tablet salut enterik ini dikemas dalam kemasan botol berisi 28 tablet yang dikemas dengan karton.

Reg. No. : DKI

HARUS DENGAN RESEP DOKTER

Dibuat oleh:

IL-YANG BIOPHARM, CO., LTD

Jecheon-si - Republic of Korea

Diimpor dan didistribusikan oleh:

PT. SANBE FARMA

Cimahi-Indonesia