PROFESSIONAL INFORMATION FOR NECTIZOLE

SCHEDULING STATUS

S4

PROPRIETARY NAMES AND DOSAGE FORM

NECTIZOLE™ 20 gastro-resistant tablet

NECTIZOLE™ 40 gastro-resistant tablet

COMPOSITION

Active ingredient:

Each **NECTIZOLE 20** gastro-resistant tablet contains 20 mg esomeprazole (as esomeprazole magnesium dihydrate).

Each **NECTIZOLE 40** gastro-resistant tablet contains 40 mg esomeprazole (as esomeprazole magnesium dihydrate).

Other ingredients:

Crospovidone, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, macrogol 6 000, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, microcrystalline cellulose, polysorbate, povidone, sodium stearyl fumarate, sugar spheres (consisting of maize starch and sucrose), talc, triethyl citrate, Opadry Pink (consisting of hypromellose, iron oxide red, iron oxide yellow, macrogol, titanium dioxide).

PHARMACOLOGICAL CLASSIFICATION

A 11.4.3 Medicines acting on gastrointestinal tract

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Esomeprazole is the S-isomer of omeprazole which reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell. Esomeprazole is a prodrug and is converted to the active form in the acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase - the acid pump. This action is dose-dependent and results in the inhibition of both basal and stimulated acid secretion.

Effect on gastric acid secretion:

The onset of effect of esomeprazole, taken orally at a dose of 20 mg and 40 mg, occurs within one hour. After repeated daily doses of 20 mg esomeprazole the mean peak acid output after pentagastrin stimulation is decreased by 90 % when measured 6 - 7 hours after dosing on day 5.

After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 is maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic gastro-oesophageal reflux disease (GORD) patients. For esomeprazole 20 mg, the proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively are about 76 %, 54 % and 24 %. Corresponding proportions for esomeprazole 40 mg are about 97 %, 92 % and 56 %.

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

Pharmacokinetic properties

Absorption and distribution

Esomeprazole is acid labile and is enteric-coated for oral administration. In vivo conversion to the R-isomer is negligible. Esomeprazole is well absorbed with peak plasma levels occurring approximately 1-2 hours after dose.

The absolute bioavailability is 89 % after repeated once-daily administration. The apparent volume of distribution at steady state in healthy subjects is approximately 0,22 l/kg body mass. 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 metabolised by the cytochrome P450 system (CYP), primarily by isoenzyme CYP2C19 which is 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.

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 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 compound is found in urine.

Special patient populations

Poor metabolisers

Approximately 1-2 % of the population lack 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 persons having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %.

Elderly patients

The metabolism of esomeprazole is not significantly changed in elderly persons (71-80 years of age).

Gender

After 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 dosage of esomeprazole.

Liver impairment

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.

Renal impairment

No data are available on 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.

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

INDICATIONS

NECTIZOLE tablets are indicated for:

Gastro-oesophageal reflux disease (GORD):

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

Patients requiring continued NSAID therapy:

- prevention of gastric and duodenal ulcers associated with NSAID (nonsteroidal anti-inflammatory drugs) therapy, in patients at risk.

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

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

NECTIZOLE may be used for pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion.

CONTRAINDICATIONS

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

Co-administration of NECTIZOLE with atazanavir or nelvinavir (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

- NECTIZOLE is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.
- Before prescribing NECTIZOLE to patients with gastric ulcers, or in the presence of symptoms such as significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena, the possibility of malignancy should be considered, since NECTIZOLE may mask symptoms and delay diagnosis.
- Symptomatic response to NECTIZOLE therapy does not preclude the presence of gastric ulcer or malignancy or a malignant disease of the oesophagus. The administration of NECTIZOLE in this situation may delay diagnoses.

Infections

NECTIZOLE may increase the risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*, because of its acid suppressive effects (see **SIDE EFFECTS**).
Clostridium difficile associated diarrhoea (CDAD), a severe debilitating diarrhoea that does not improve, may occur. Symptoms may include watery stools, abdominal pain, fever and patients may develop more serious intestinal conditions.
A diagnosis of CDAD should be considered in patients with diarrhoea that does not improve. Patients should be advised to seek immediate medical attention if they experience watery stools, abdominal pain and fever while taking NECTIZOLE.
The lowest dose for the shortest duration of therapy, appropriate for the condition being treated, should be used.

Fractures

Proton pump inhibitors, like NECTIZOLE, especially in prolonged use (>1 year) and in high doses, may increase the risk of fractures of the hip, wrist and spine (see **SIDE EFFECTS**). This is of special importance in the elderly or in the presence of other recognised risk factors. 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.

Other effects of acid inhibition

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. During long-term treatment with antisecretory medicines, gastric glandular cysts have been reported to occur at an increased frequency due to long-term acid inhibition (see **SIDE EFFECTS**).

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

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like NECTIZOLE for at least three months, and in most cases for a year. Severe hypomagnesaemia can correlate with hypocalcaemia. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular dysrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take NECTIZOLE with digoxin or medicines that may cause hypomagnesaemia (e.g., diuretics), it could be considered to measure magnesium levels before starting PPI treatment and periodically during treatment.

Hepatic impairment

In patients with cirrhosis of the liver increases in esomeprazole bioavailability and elimination half-lives have been reported. For dosage adjustment in patients with hepatic impairment, refer to **DOSAGE AND DIRECTIONS FOR USE**.

NECTIZOLE should be used with caution in hepatic impairment.

Special precautions

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

Effects on ability to drive and use machines

NECTIZOLE is not likely to affect the ability to drive or use machines. Some patients may experience blurred vision, dizziness or vertigo (see **SIDE EFFECTS**) and should not drive or handle machines if that is the case.

INTERACTIONS

NECTIZOLE is metabolised via the hepatic P450 cytochrome enzyme system, which may affect the metabolism of other medications metabolised by these enzymes when given concomitantly.

Effects of NECTIZOLE on the pharmacokinetics of other medicines:

Medicines with pH dependent absorption:

NECTIZOLE, by inhibiting gastric acid secretion, has the potential to affect the bioavailability of any medicine with pH dependant absorption, such as protease inhibitors and antifungal agents.

Protease inhibitors: Increased gastric pH during NECTIZOLE treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19. NECTIZOLE should not be used concomitantly with nelfinavir (plasma levels are increased). Concomitant use with atazanavir is not recommended; decreased serum levels of atazanavir may result (see **CONTRAINDICATIONS**).

Triazole antifungal medications: The decreased intragastric acidity during treatment with NECTIZOLE might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity. The absorption of ketoconazole and itraconazole can decrease during treatment with NECTIZOLE.

The plasma concentration of both esomeprazole, contained in NECTIZOLE, and voriconazole (a CYP2C19 substrate) may be increased and a reduced dose of NECTIZOLE is recommended, particularly in patients with severe hepatic impairment and if long-term treatment is indicated.

Dasatinib:

NECTIZOLE can reduce the absorption of dasatinib, as its absorption is pH dependant.

Medicines metabolised by CYP2C19:

NECTIZOLE inhibits CYP2C19, the major esomeprazole metabolising enzyme. Concomitant administration with medicines metabolised by CYP2C19, such as diazepam, imipramine, clomipramine, citalopram, phenytoin etc., may increase the plasma concentrations of these medicines and a dose reduction could be needed. The plasma concentrations of phenytoin should be monitored when treatment with NECTIZOLE is introduced or withdrawn.

Cisapride:

Concomitant administration of NECTIZOLE and cisapride increases the exposure to cisapride and prolongs its elimination half-life (t½). This interaction did not alter the influence of cisapride on cardiac electrophysiology.

Anticoagulants:

Clinically significant elevated INR has been reported with NECTIZOLE. Monitoring of INR serum levels is recommended and dosage reductions may be necessary when NECTIZOLE is given concomitantly with warfarin or other anticoagulants.

Clopidogrel

Clopidogrel is metabolised by CYP2C19. NECTIZOLE may reduce its antiplatelet effect due to esomeprazole's competitive inhibition of CYP2C19. There is a possible increased risk of cardiovascular events when NECTIZOLE is used with clopidogrel. Concomitant use of NECTIZOLE and clopidogrel is therefore not advisable.

Digoxin:

There is a possible interaction of NECTIZOLE with digoxin and a 10 % increase in digoxin bioavailability may be expected.

Iron salts:

NECTIZOLE may decrease the absorption of orally-administered iron salts.

Nonsteroidal anti-inflammatory drugs (NSAIDs):

No clinically relevant side effects have been recorded between NECTIZOLE and naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID).

Methotrexate:

NECTIZOLE may elevate serum concentrations of methotrexate and may be associated with delayed plasma elimination of methotrexate in patients given high-dose methotrexate therapy. In high-dose therapy with methotrexate a temporary withdrawal of NECTIZOLE may need to be considered.

Effects of other medicines on the pharmacokinetics of NECTIZOLE:

Inhibitors of CYP3A4:

- Clarithromycin is a potent inhibitor of CYP3A4 and NECTIZOLE is also metabolised via CYP3A4. Concomitant administration of NECTIZOLE and clarithromycin increases plasma levels of esomeprazole and 14-hydroxyclarithromycin. Dose adjustment of NECTIZOLE is not required.
- No clinical relevant interactions occur with amoxicillin.

Inducers of CYP2C19 or CYP3A4:

Medicines known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Laboratory tests

NECTIZOLE may cause false-negative results in the urea breath test of *Helicobacter pylori* infection.

Investigations

Increased chromogranin A (CgA) levels may interfere with investigations for neuroendocrine tumours. To avoid this interference, NECTIZOLE treatment should be temporarily stopped for at least five days before CgA measurements.

PREGNANCY AND LACTATION

Safety during pregnancy and breast-feeding has not been determined.

DOSAGE AND DIRECTIONS FOR USE

Dosage for adults and adolescents from the age of 12 years:

See dosage schedules below; take all doses at least 30 minutes before a meal.

Gastro-oesophageal reflux disease (GORD)

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 only, an on demand regimen of 20 mg taken once daily, when needed, can be used.

Patients requiring continuous NSAID therapy:

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

- 20 mg or 40 mg once daily.

Helicobacter pylori:

In combination with an appropriate antibacterial therapeutic regimen:

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

Pathological hypersecretory conditions including Zollinger-Ellison syndrome and idiopathic hypersecretion:

The recommended initial dosage is 40 mg of NECTIZOLE twice daily. The dosage should then be individually adjusted and treatment continued as long as clinically indicated. Doses up to 120 mg twice daily have been given.

Dosage for children below the age of 12 years

NECTIZOLE should not be used in children younger than 12 years since no data are 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 (see **Pharmacokinetic properties**).

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 NECTIZOLE should not be exceeded (see **Pharmacokinetic properties**).

Elderly patients (above 65 years)

Dose adjustment is not required in the elderly.

Directions for use:

The tablets should be swallowed whole with water. The tablets should not be chewed or crushed.

For patients who have difficulty in swallowing, the tablets may be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coat may be dissolved. The tablets should be stirred until they disintegrate and the liquid with the pellets should be drunk immediately. The empty glass should be rinsed with half a glass of water and swallowed. 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.

SIDE EFFECTS

Infections and infestations

Less frequent: Gastrointestinal or oesophageal candidiasis, respiratory infection, sinusitis.

Frequency unknown: Pancreatitis.

Neoplasms benign and malignant (including cysts and polyps)

Frequency unknown: Gastric glandular cysts (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Blood and the lymphatic system disorders

Less frequent: Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia.

Immune system disorders

Less frequent: Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders

Less frequent: Peripheral oedema, hyponatraemia.

Frequency unknown: Hypomagnesaemia (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Psychiatric disorders

Less frequent: Insomnia, agitation, confusion, somnolence, depression, aggression, hallucination.

Nervous system disorders

Frequent: Headache.

Less frequent: Dizziness, paraesthesia, somnolence, taste disturbance, fatigue.

Eye disorders

Less frequent: Blurred vision.

Ear and labyrinth disorders

Less frequent: Vertigo.

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm.

Gastrointestinal disorders

Frequent: Abdominal pain, diarrhoea, flatulence, constipation, nausea/vomiting, dyspepsia.

Less frequent: Dry mouth, stomatitis.

Frequency unknown: Microscopic colitis.

Hepatobiliary disorders

Less frequent: Increased liver enzymes, hepatitis with or without jaundice, hepatic failure, hepatic encephalopathy.

Skin and subcutaneous tissue disorders

Less frequent: Dermatitis, pruritus, rash, urticaria, alopecia; photosensitivity, bullous eruption.

Frequency unknown: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN).

Musculoskeletal, connective tissue and bone disorders

Less frequent: Arthralgia, myalgia, muscular weakness, fractures of the hip, wrist and spine (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Renal and urinary disorders

Less frequent: Interstitial nephritis.

Reproductive system and breast disorders

Less frequent: Gynaecomastia.

General disorders and administration site conditions

Less frequent: Malaise, increased sweating.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdosage may include gastrointestinal symptoms and weakness.

No specific antidote is known. NECTIZOLE is extensively plasma protein bound and is therefore not readily dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

IDENTIFICATION

NECTIZOLE 20: Light pink coated 6,55 x 13,6 mm, elliptically shaped, biconvex gastro-resistant tablet.

NECTIZOLE 40: Pink coated 8,2 x 17 mm, elliptically shaped, biconvex gastro-resistant tablet.

PRESENTATION

NECTIZOLE 20 and NECTIZOLE 40 gastro-resistant tablets are packed in one of the following packaging materials, in packs containing 14, 28 or 30 tablets:

- Blister strips consisting of a silver coloured plain aluminium foil and silver coloured cold forming blister aluminium foil (Alu/Alu blister) in an outer carton.
- Blister strips consisting of a silver coloured plain aluminium foil and clear colourless PVC/PVDC foil in an outer carton.
- White round HDPE containers with a desiccant and closed with white round LDPE lids in an outer carton.

Not all pack sizes are necessarily marketed at any one time.

STORAGE INSTRUCTIONS

Store at or below 25 °C in a dry place in the original packaging. Keep blisters in the carton until required for use. Keep container tightly closed.

REGISTRATION NUMBERS

NECTIZOLE 20: 48/11.4.3/0438
NECTIZOLE 40: 48/11.4.3/0439

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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