PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

NEXES OTC gastric-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NEXES OTC:

Each gastric-resistant tablet contains esomeprazole magnesium equivalent to 20 mg esomeprazole.

Contains sugar sucrose 9,99 to 14,63 mg and lactose monohydrate 31,875 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastric-resistant tablets.

NEXES OTC:

Brick red coloured, round shaped, biconvex, film-coated tablet imprinted with "20" on one side with black ink and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NEXES OTC is indicated for the temporary, short-term relief of heartburn and hyperacidity subject to:

a) a maximum daily dose of 20 milligrams

b) a maximum treatment period of 14 days.

4.2 Posology and method of administration

Posology

Heartburn and hyperacidity

The recommended dose is 20 mg esomeprazole (one tablet) per day.

- It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms. The duration of treatment is up to 2 weeks. Once complete relief of symptoms has occurred, treatment should be discontinued.
- If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

Special populations

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 daily dose of 20 mg NEXES OTC should be used.

Elderly:

Dose adjustment is not required in the elderly.

Paediatric population

NEXES OTC should not be used in children younger than 1 year since no data is available.

Method of administration

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

4.3 Contraindications

- Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of NEXES OTC (see section 6.1).
- Concomitant administration of NEXES OTC with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

NEXES OTC is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

Prior to treatment or in the presence of any alarming symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with NEXES OTC may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

There is an increased risk of subclinical acute interstitial nephritis (AIN) associated with proton pump inhibitors (PPIs), such as NEXES OTC, which may progress to acute kidney injury and/or chronic renal failure. Symptoms of interstitial nephritis may persist even when treatment with the PPI is terminated.

Patients on on-demand treatment should be instructed to contact their medical practitioner if their symptoms change in character.

During long-term oral treatment with esomeprazole, gastric glandular cysts occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign, and appear to be reversible.

Esomeprazole, as all acid blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases, for a year. 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 PPIs with digoxin or medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Proton pump inhibitors, especially if used in high doses and over long durations (> 1 year), may

modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10 – 40 %. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have adequate intake of vitamin D and calcium.

Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping NEXES OTC. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Concomitant administration of clopidogrel and esomeprazole resulted in decreased exposure to the active metabolite of clopidogrel by an average of 40 %. The maximum inhibition of (ADP induced) platelet aggregation decreased by an average of 14 %. Based on these data, concomitant use of NEXES OTC and clopidogrel should be avoided.

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference, the esomeprazole treatment should be temporarily stopped 5 days before CgA measurements.

Special Precautions:

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

Decreased gastric acidity due to any means including proton pump inhibitors such as NEXES OTC tablets, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with NEXES OTC may lead to increased risk of gastrointestinal infections such as Salmonella and Campylobacter and also Clostridium difficile in hospitalised patients.

Clostridium difficile is a bacterium that can cause severe debilitating diarrhoea that does not improve.

Symptoms may include watery stools, abdominal pain, fever, and patients may develop more serious intestinal conditions.

Excipient warning

NEXES OTC tablets contain sucrose and lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption, sucrase-isomaltase deficiency or fructose intolerance should not take NEXES OTC.

4.5 Interaction with other medicines and other forms of interaction

Effects of NEXES OTC on the pharmacokinetics of other medicines:

The gastric acid suppression during treatment with NEXES OTC, might decrease or increase the absorption of medicines with a gastric pH dependent absorption. The absorption of medicines such as ketoconazole, itraconazole and erlotinib can decrease while the absorption of medicines such as digoxin can increase during treatment with NEXES OTC.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10 % (up to 30 % in 2 out of 10 subjects). Digoxin toxicity has been reported. Caution should be exercised when NEXES OTC is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

From post marketed use, cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when warfarin is co-administered with NEXES OTC at initiation of treatment, during the treatment and at ending of treatment.

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19.

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration, a temporary withdrawal of NEXES OTC may need to be considered.

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

Studies evaluating concomitant administration of NEXES OTC and either naproxen (nonselective NSAID) or rofecoxib (COX-2-selective NSAID) did not identify any clinically relevant interaction.

Concomitant administration of NEXES OTC may significantly reduce the plasma levels of atazanavir.

Omeprazole has been reported to interact with some antiretroviral medicines. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral medicines. Other possible interaction mechanisms are via CYP2C19. For some antiretroviral medicines, such as atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended.
NEXES OTC substantially decreases the concentration of nelfinavir. Concomitant administration of esomeprazole and antiretroviral medicines such as atazanavir and nelfinavir is not recommended.
For other antiretroviral medicines, such as saquinavir, increased serum levels have been reported of 80-100 %. There are also some antiretroviral medicines for which unchanged serum levels have been reported when given with omeprazole. Close monitoring or dose alteration is recommended.

Tipranavir may decrease the concentration of NEXES OTC. Co-administration is not recommended. However, if used concurrently, the dose of NEXES OTC should be increased.

Effects of other medicines on the pharmacokinetics of NEXES OTC:
NEXES OTC is metabolised by CYP2C19 and CYP3A4. Concomitant administration of NEXES OTC and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to NEXES OTC.
Concomitant administration of NEXES OTC and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the NEXES OTC exposure.
Dose adjustment of NEXES OTC is not required.
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**.**

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established.

Breast-feeding

Safety during lactation has not been established.

4.7 Effects on ability to drive and use machines

NEXES OTC may cause dizziness and blurred vision, thereby affecting the ability to drive or use machinery.

4.8 Undesirable effects

a. 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 post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations.

b. Summary of adverse reactions

Blood and lymphatic system disorders

Less Frequent: Leukopenia, thrombocytopenia

Immune System Disorders

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

Metabolism and nutrition disorders

Less Frequent: Peripheral oedema, Hyponatraemia, Hypomagnesaemia

Frequency Unknown: Severe hypermagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia

Psychiatric Disorders

Less Frequent: Insomnia, agitation, confusion, depression, aggression, hallucination.

Nervous System Disorders

Frequent: Headache

Less Frequent: Dizziness, paraesthesia, somnolence, taste disturbance

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, nausea/vomiting, constipation, fundic gland polyps (benign)

Less Frequent: Dry mouth, stomatitis, gastrointestinal candidiasis, gastrointestinal infections, microscopic colitis

Hepatobiliary disorders

Less Frequent: Increased liver enzymes, hepatitis with or without jaundice, hepatic encephalopathy

Skin and Subcutaneous Tissue Disorders

Less Frequent: Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity

Frequency Unknown: Subacute cutaneous lupus erythematosus

Musculoskeletal and connective tissue Disorders

Less Frequent: Arthralgia, myalgia, muscular weakness.

Renal and urinary disorders

Less Frequent: Interstitial nephritis, may progress to acute kidney injury and/or chronic renal failure; in some patient's renal failure has been reported concomitantly

Reproductive system and breast disorders

Less Frequent: Gynaecomastia

General disorders and administration site conditions

Less Frequent: Malaise, hyperhidrosis

Post marketing experience

Blood and lymphatic system disorders:

Leukopenia, thrombocytopenia, agranulocytosis, pancytopenia

Immune system disorders:

Hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders:

Peripheral oedema, hyponatraemia

Psychiatric disorders:

Insomnia, agitation, confusion, depression, aggression, hallucination

Nervous system disorders:

Headache, dizziness, paraesthesia, somnolence, taste disturbance

Eye disorders:

Blurred vision

Ear and labyrinth disorders:

Vertigo

Respiratory, thoracic and mediastinal disorders:

Bronchospasm

Gastrointestinal disorders:

Abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation, dry mouth, stomatitis, gastrointestinal candidiasis.

Hepatobiliary disorders:

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

Skin and subcutaneous tissue disorders:

Dermatitis, pruritus, urticaria, rash, alopecia, photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders:

Arthralgia, myalgia, muscular weakness

Renal and urinary disorders:

Interstitial nephritis

Reproductive system and breast disorders:

Gynaecomastia

General disorders and administration site conditions:

Malaise, hyperhidrosis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows

continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. You can also report side effects to Acino Pharma via email on drugsafety_ZA@acino.swiss.

4.9 Overdose

No specific antidote is known. NEXES OTC is extensively plasma protein bound and is therefore not readily dialysable. 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: Drugs for acid-related disorders, proton pump inhibitor.

ATC code A02B C05.

Mechanism of Action:

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell, where it is concentrated and converted to the active form in the acidic environment of the secretory canaliculi and inhibits the enzyme H+K+-ATPase – the acid pump. This effect on the final step of the gastric acid secretion is dose-dependent and provides for effective inhibition of both basal and stimulated acid secretion.

Effect on gastric acid secretion:

After oral dosing with esomeprazole 20 mg, the onset of effect occurs within 1 hour. After repeated administration with 20 mg esomeprazole once daily for 5 days, 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 of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic Gastro-oesophageal Reflux Disease (GORD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were 76 %, 54 % and 24 % respectively for esomeprazole 20 mg.

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

Food intake had no significant influence on the effect of esomeprazole on intragastric acidity.

Other effects related to acid inhibition:

During long-term treatment with antisecretory medicines, gastric glandular cysts occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

5.2 Pharmacokinetic properties

Absorption

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 89 % after repeated once-daily administration.

For 20 mg esomeprazole the corresponding values are 50% and 68% respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0,22 litres/kg body weight. Esomeprazole is 97 % plasma protein bound.

Biotransformation

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.

Elimination

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

Total plasma clearance is about 17 litres per hour after a single dose and about 9 litres per hour 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 non-linear dose-AUC relationship 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 2,9 ± 1,5 % 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.

Hepatic insufficiency:

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 insufficiency:

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.

Elderly:

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

Paediatric population

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Copovidone K-28

Crospovidone (E1202)

Diethyl phthalate

Ethyl cellulose (E462)

Ferric oxide red (E172)

Hypromellose

Light magnesium oxide (E530)

Macrogol 8000

Magnesium stearate (E572)

Methacrylic acid-ethyl acrylate copolymer (11) dispersion 30 per cent

Povidone K-90

Silicified microcrystalline cellulose (microcrystalline cellulose and colloidal anhydrous silica)

Starlac (lactose monohydrate and maize starch)

Sugar spheres (sucrose and maize starch)

Talc (purified) (E553b)

Titanium dioxide (E171)

Imprinting ink

Black iron oxide (E172)

Shellac glaze (E904)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30°C.

Store in the original package in order to protect from light and moisture.

Keep out of reach of children.

6.5 Nature and contents of container

NEXES OTC tablets are packed in following packs

- *Aluminum – Aluminum blisters*

Alu-Alu blister pack using aluminium foil with heat seal lacquer and cold formable blister aluminium foil. The blister strips will be packed in an outer carton.

Pack size 14 or 28's.

- *HDPE containers*

HDPE container pack using High – Density Polyethylene [HDPE] container of neck finish and CT closure with induction sealing wad.

Pack size 14, 28, 56, or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

8 REGISTRATION NUMBER(S)

NEXES OTC: 48/11.4.2/1116

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 December 2021

10 DATE OF REVISION OF THE TEXT

01 February 2024