Approved Professional Information for Medicines for Human Use:

NEXTELL OTC

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

NEXTELL OTC Gastro-Resistant Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEXTELL OTC:

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

Contains Sugar spheres NF (mesh 60/ 80) (sucrose):

NEXTELL OTC: Each Gastro-resistant tablet contains 6,14 mg sugar spheres NF (mesh 60/ 80).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets

NEXTELL OTC Gastro-resistant tablet

A light pink, 6,55 x 13,6 mm, elliptically shaped, biconvex, enteric-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of reflux symptoms such as heartburn and regurgitation in adults.

4.2 Posology and method of administration

Posology

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 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. However, patients with severe liver impairment should be advised by a doctor before taking NEXTELL OTC.

Elderly:

Dose adjustment is not required in the elderly.

Paediatric population

There is no relevant use of NEXTELL OTC in the paediatric population below 18 years of age for the indication of "short-term treatment of reflux symptoms (e.g., heartburn and acid regurgitation)".

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 NEXTELL OTC (see section 6.1).

Concomitant administration of NEXTELL OTC. with atazanavir or nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

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

Prior to treatment or in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, the possibility of malignancy of gastric ulcer or a malignant disease of the oesophagus should be excluded, as the treatment with NEXTELL 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 NEXTELL 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 should be instructed to consult a doctor if:

- They have had previous gastric ulcer or gastrointestinal surgery.
- They have been on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Concomitant administration with NEXTELL OTC. and medicines such as atazanavir and nelfinavir is not recommended (see sections 4.3 and 4.5).
Therapeutic medicine monitoring is recommended during concomitant treatment with warfarin (see section 4.5).

NEXTELL OTC, 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.

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 NEXTELL OTC. and clopidogrel should be avoided.

During treatment with NEXTELL OTC. serum gastrin increases, in response to decreased acid secretion.

Proton pump inhibitors are associated with very infrequent cases of sub-acute cutaneous lupus erythematosus (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 NEXTELL OTC. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

During treatment with antisecretory medicines, serum gastrin increases in response to the decreased acid secretion. Also, chromogranin A (CgA) increase 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. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

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.

Patients should not take NEXTELL OTC. as a long-term preventive medicinal product.

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

Excipient sucrose

This medicine contains sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effects of NEXTELL OTC *on the pharmacokinetics of other medicines:*

The gastric acid suppression during treatment with NEXTELL 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 NEXTELL 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 NEXTELL OTC is given at high doses in elderly patients. Therapeutic monitoring of digoxin levels should be done.

NEXTELL OTC inhibits CYP2C19, the major NEXTELL OTC metabolising enzyme. Concomitant administration of 30 mg NEXTELL OTC resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance. Concomitant administration of 40 mg NEXTELL OTC resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients.

Concomitant administration of 40 mg NEXTELL OTC to warfarin-treated patients showed that, despite elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range.

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 NEXTELL OTC at initiation of treatment, during the treatment and at ending treatment.

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40 % and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14 %. Based on these data, concomitant use of NEXTELL OTC and clopidogrel should be avoided.

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18 % and 26 % respectively, and one of its metabolites

by 29 % and 69 % respectively. NEXTELL OTC can be suspected to have a similar effect.

In concomitant administration of 40 mg NEXTELL OTC resulted in a 32 % increase in area under the plasma concentration-time curve (AUC) and a 31 % prolongation of elimination half-life (t½) but no significant increase in peak plasma levels of cisapride. This interaction did not alter the influence of cisapride on cardiac electrophysiology.

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 NEXTELL OTC may need to be considered.

Concomitant administration of NEXTELL OTC has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

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

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

Concomitant administration of NEXTELL 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.

Co-administration of esomeprazole (40 mg once daily) reduced mean nelfinavir exposure by approximately 40 % and the mean exposure of the pharmacological active metabolite was reduced by approximately 75-90 %. NEXTELL OTC substantially decreases the concentration of nelfinavir Concomitant administration with 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 NEXTELL OTC. Co-administration is not recommended. However, if used concurrently, the dose of NEXTELL OTC should be increased.

Effects of other medicines on the pharmacokinetics of NEXTELL OTC*:*
NEXTELL OTC is metabolised by CYP2C19 and CYP3A4. Concomitant administration of NEXTELL OTC and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to NEXTELL OTC.

Concomitant administration of NEXTELL OTC and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than tripling of the NEXTELL OTC exposure.

Dose adjustment of NEXTELL 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.

Breastfeeding

Safety during lactation has not been established.

4.7 Effects on ability to drive and use machines

NEXTELL 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) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with esomeprazole.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		*Clostridium difficile* associated diarrhoea.	
Blood and lymphatic system disorders		Leukopenia, thrombocytopenia	Agranulocytosis, pancytopenia

Immune system disorders		Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction / shock	
Metabolism and nutrition disorders		Peripheral oedema, Hyponatraemia, Hypomagnesaemia	Severe hypermagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders		Insomnia, Agitation, reversible confusional state, 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, fundic gland polyps (benign)	Dry mouth, stomatitis, taste disturbance, gastrointestinal candidiasis, gastrointestinal infections	Microscopic colitis
Hepatobiliary disorders		Increased liver enzymes, Hepatitis with or without jaundice	Hepatic encephalopathy in patients with pre-existing liver disease, hepatic failure
Skin and subcutaneous tissue disorders	Skin rashes	Dermatitis, pruritus, urticaria, rash, alopecia, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), photosensitivity	Subacute cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, Muscular weakness.	
Renal and urinary disorders		Interstitial nephritis, in some patient's renal failure has been reported concomitantly, may progress to acute kidney injury and/or chronic renal failure.	
Reproductive system and breast disorders		Gynaecomastia	
General disorders and administration site conditions		Malaise, fatigue, 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 drug

reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

No specific antidote is known. NEXTELL 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

Pharmacological classification: A 11.4.3 Medicines acting on gastric-intestinal tract. Other.

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 and 40 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 and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic 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. Corresponding proportions for esomeprazole 40 mg were 97 %, 92% and 56% respectively.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown. (1C:2)

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.

Metabolism

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 I % of the parent compound is found in urine.

Special 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. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100 % higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of esomeprazole.

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.

Gender

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

Elderly

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellet excipients

Glycerol Monostearate 40-55 (type II)

Hydroxypropyl Cellulose

Hypromellose (2910 (3 cPs))

Magnesium Stearate NF

Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 %

Polysorbate 80 NF

Sugar spheres NF (mesh 60 /80)

Talc

Triethyl citrate

Tablet core:

Crospovidone (type A)

Macrogol 6000

Microcrystalline Cellulose

Povidone K-29/32

Sodium stearyl fumarate

Film-coating solution (% w/w):

Hypromellose (2910 (6 cPs)), Iron oxide red (E172), Iron oxide yellow (E172), Macrogol (PEG 400), Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Alu/Alu blister: 24 months.

HDPE containers with desiccant: 24 months.

6.4 Special precautions for storage

Store at or below 30 °C. Store in a dry place.

Store in the original packaging to protect from moisture.

6.5 Nature and contents of container

NEXTELL OTC are packed in Alu/Alu blister packs in pack sizes of 7, 10, and 14 tablets or are packed in HDPE containers with desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

NEXTELL OTC: 59/11.4.3/0222

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

06 February 2024

10. DATE OF REVISION OF THE TEXT

11 March 2025