PROFESSIONAL INFORMATION:

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE:

NEXILOK 20, gastro-resistant tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

NEXILOK 20: Each gastro-resistant tablet contains esomeprazole magnesium dihydrate 21,75 mg (equivalent to esomeprazole 20 mg) in the form of a multiple unit pellet system.

Each tablet contains no more than 5,65 mg of sucrose.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Gastro-resistant tablets

NEXILOK 20: A light pink, elliptically shaped, biconvex enteric-coated tablet, 6,55 x 13,6 mm.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

NEXILOK is indicated for:

Temporary, short-term relief of heartburn and hyperacidity.

4.2 Posology and method of administration:

Posology:

The recommended dose is 20 mg (one tablet) daily, for a maximum treatment period of 14 days.

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 14 days 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 (see **section 5.2**).

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 NEXILOK should be used (see **sections 4.4** and **5.2**).

Elderly:

Dose adjustment is not required in the elderly.

Paediatric population:

There is no experience with NEXILOK in the paediatric population below 18 years of age.

Method of administration:

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

The tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. 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.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

General:

Patients should be instructed to consult a doctor if:

- They have significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena and when gastric ulcer is suspected or present, malignancy should be excluded, as the treatment with NEXILOK may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.
- They have had previous gastric ulcer of 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.

Patients should not take NEXILOK as a long-term preventative medicine:

Treatment with proton pump inhibitors such as NEXILOK may lead to slightly increased risk of gastric intestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile* (see **section 5.1**).

PPI therapy like esomeprazole as contained in NEXILOK may be associated with an increased risk of *Clostridium difficile* associated with watery diarrhoea, stomach pain and fever, especially in hospitalised patients. Patient should consult their doctor before taking this medicine if they are due to have an endoscopy or urea breath test.

Subacute cutaneous lupus erythematosus (SCLE):

Proton pump inhibitors are associated with very infrequent cases of subacute 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 healthcare professional should consider stopping NEXILOK. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Combination with other medicines:

Co-administration of esomeprazole, as contained in NEXILOK, with atazanavir and nelfinavir is contraindicated (see **section 4.3**) and clopidogrel (see **section 4.5**).

NEXILOK is a CYP2C19 inhibitor. When starting or ending treatment with NEXILOK, the potential for interactions with medicines metabolised through CYP2C19 should be considered.

Patients should not take another PPI or H_2 antagonist concomitantly.

Renal failure:

Interstitial nephritis may progress to chronic renal inflammation and renal failure as it is not necessarily reversed when treatment is discontinued.

Interference with laboratory tests:

Increased Chromagranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, NEXILOK treatment should be stopped for at least 5 days before CgA measurements (see **section 5.1**). If CgA and gastrin levels have not returned to reference range after initial measurements, it should be repeated 14 days after cessation of proton pump inhibitor treatment.

Sucrose:

NEXILOK contains sugar (sucrose). Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take NEXILOK.

Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction:

Interaction studies have only been performed in adults.

Effects of NEXILOK on the pharmacokinetics of other medicines:

As esomeprazole, contained in NEXILOK, is one enantiomer of omeprazole it is reasonable to advise about interactions reported with omeprazole.

Protease inhibitors:

Increased gastric pH during omeprazole treatment my change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

Atazanavir & nelfinavir:

Esomeprazole, contained in NEXILOK, decreases the concentration of atazanavir and nelfinavir. Co-administration of NEXILOK and atazanavir or nelfinavir is contraindicated (see **section 4.3**).

For saquinavir (with concomitant ritonavir), increased serum levels (80 - 100 %) have been reported during concomitant omeprazole treatment (40 mg once a day).

Treatment with omeprazole 20 mg once a day had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).

Treatment with esomeprazole 20 mg, as contained in NEXILOK, once a day had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once a day had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate:

When given together with proton pump inhibitors (PPI's) such as NEXILOK, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of NEXILOK may need to be considered.

Tacrolimus:

Concomitant administration of esomeprazole as in NEXILOK 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.

Medicines with pH dependent absorption:

The decreased intragastric acidity during treatment with NEXILOK, might increase or decrease the absorption of medicines if the mechanism of absorption is influenced by gastric acidity. The absorption of ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with NEXILOK. Caution should be exercised when NEXILOK is given at high doses in elderly patients. Therapeutic monitoring of digoxin should be reinforced.

Medicines metabolised by CYP2C19:

Esomeprazole, contained in NEXILOK, inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when NEXILOK is combined with medicines metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicines may be increased and a dose reduction could be needed. This should be considered especially when prescribing NEXILOK for on demand therapy.

Diazepam:

Concomitant administration of 30 mg esomeprazole resulted in a 45 % decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin:

Concomitant administration of 40 mg esomeprazole resulted in a 13 % increase in trough plasma levels of phenytoin in epileptic patients; dose adjustment was not required.

Voriconazole:

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC by 15 % and 41 %, respectively.

Cilostazol:

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 C_{max} and AUC for cilostazol by 18 % and 26 % respectively, and one of its active metabolites by 29 % and 69 % respectively.

Warfarin:

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

However, as with all patients receiving warfarin, monitoring is recommended during concomitant treatment with NEXILOK.

Clopidogrel:

Studies in healthy subjects have shown that concomitant use of clopidogrel and esomeprazole resulted in decreased plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. An increase in cardiovascular events has also been reported. Concomitant use of NEXILOK and clopidogrel should be avoided.

Cisapride:

In healthy volunteers, concomitant administration of 40 mg NEXILOK 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.

Effects of other medicines on the pharmacokinetics of NEXILOK:

Medicines which inhibit CYP2C19 and/or CYP3A4:

NEXILOK is metabolised by CYP2C19 and CYP3A4. Concomitant administration of NEXILOK and a CYP3A4 inhibitor, clarithromycin (500 mg twice daily), resulted in a doubling of the exposure (AUC) to esomeprazole, contained in NEXILOK.

Dose adjustment of NEXILOK is not required.

Medicines which induce CYP2C19 and/or CYP3A4:

Medicines known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's Wort *(Hypericum perforatum)*) 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.

Fertility:

Reported animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines:

NEXILOK may cause somnolence, dizziness and blurred vision. As concentration may be impaired, patients should be advised to exercise caution when driving or operating machinery (see **section 4.8**).

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. No dose-related adverse reactions have been identified.

b. Tabulated summary of adverse reactions:

Infections and infestations:	
Less frequent	*Clostridium difficile* associated diarrhoea
Blood and lymphatic system disorders:	
Less frequent	Leukopenia, thrombocytopenia
Frequency unknown	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, severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders:	
Less frequent	Insomnia, agitation, reversible confusional state, depression
Frequency unknown	Aggression, hallucinations
Nervous system disorders:	
Frequent	Headache
Less frequent	Dizziness, paraesthesia, somnolence
Frequency unknown	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, constipation, diarrhoea, flatulence, nausea/vomiting
Less frequent	Dry mouth, stomatitis, gastrointestinal candidiasis
Frequency unknown	Microscopic colitis
Hepato-biliary disorders:	
Less frequent	Increased liver enzymes, hepatitis with or without jaundice
Frequency unknown	Hepatic encephalopathy, hepatic failure

Skin and subcutaneous tissue disorders:	
Frequent	Skin rashes
Less frequent	Dermatitis, pruritus, rash, urticaria, alopecia, bullous eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), photosensitivity
Frequency unknown	Subacute cutaneous lupus erythematosus (see **section 4.4**)
Musculoskeletal and connective tissue disorders:	
Less frequent	Arthralgia, myalgia, fracture of hip, wrist or spine or muscular weakness
Renal and urinary disorders:	
Less frequent	Interstitial nephritis
Frequency unknown	Renal failure
Reproductive system and breast disorders:	
Less frequent	Gynaecomastia
General disorders and administration site conditions:	
Less frequent	Malaise, hyperhidrosis, fatigue

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. Healthcare 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.

4.9 Overdose:

The symptoms described in connection with deliberate NEXILOK overdose (limited experience of doses in excess of 280 mg/day) are transient.

No specific antidote is known. Esomeprazole contained in NEXILOK 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.

5. PHARMACOLOGICAL PROPERTIES:

A 11.4.3 Medicines acting on gastro-intestinal tract. Other.

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Drugs for acid-related disorders proton pump inhibitors

ATC code: A02B C05

Esomeprazole, the S-isomer of omeprazole, reduces gastric acid secretion through specific inhibition of the acid pump in the parietal cell.

Mechanism of action:

Esomeprazole is a weak base and is concentrated and 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. It inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects:

After oral dosing with esomeprazole 20 mg and 40 mg, the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90 % when measured 6 – 7 hours after dosing on day 5.

After five 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.

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 treatment with antisecretory medicines serum gastrin increases in response to the decreased acid secretion. Decreased gastric acidity due to any means including PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile* (see **section 4.4**).

Clinical efficacy:

In the reported two multicentre, randomized, double-blind, placebo-controlled pivotal studies 234 subjects with a recent history of frequent heartburn were treated with 20 mg esomeprazole for 4 weeks. Symptoms associated with acid reflux (such as heartburn and acid regurgitation) were evaluated according to standard methodology. In both studies esomeprazole 20 mg was significantly better compared to placebo for the primary endpoint, complete resolution of heartburn ($p < 0.001$) and for the secondary endpoints such as relief of heartburn, days without heartburn and mean heartburn severity scoring. This applies for all of the time points 1, 2 and 4 weeks of treatment and for both day and night time scoring with increasing treatment effect by time. Furthermore, approximately 78 % of the subjects on esomeprazole reported first resolution of heartburn within the first week of treatment.

The median time to first resolution of night-time heartburn was 1 day. About 80 % of nights were heartburn free during all time periods and 90 % of nights were heartburn free by week 2 of each trial.

Subjects also demonstrated relief of reflux symptoms other than heartburn, including regurgitation (58,5 % - 63,6 % showed relief during week 2 evaluation). Following Overall Treatment Evaluation (OTE) of patients at week 2, 78,0 - 80,7 % of patients, reported their condition as improved. The majority of

these rated the importance of this change to be Important to Extremely Important in performing their activities of daily living (79 - 86 % at week 2).

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.

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.

Linearity/Non-linearity:

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.

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 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 liver dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing.

Renal impairment:

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 patients:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Pellets:

Glycerol monostearate 40-55 (type II)

Hydroxypropyl cellulose

Hypromellose

Magnesium stearate NF

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

Microcrystalline cellulose

Polysorbate 80

Sugar spheres NF (sucrose and maize starch)

Talc

Triethyl citrate

Tablet core:

Crospovidone (type A)

Macrogol 6000

Microcrystalline cellulose

Povidone K-29/32

Sodium stearyl fumarate

Tablet coating:

Opadry Pink 03B34284/5 consisting of:

Hypromellose

Titanium dioxide (E171)

Macrogol (PEG 400)

Iron oxide red (E172)

Iron oxide yellow (E172)

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

2 years

6.4 Special precautions for storage:

Do not store above 30 °C.

Store in the original package (blister) in order to protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container:

OPA/Aluminium/PVC - Aluminium foil blisters.

Pack sizes: 7, or 14 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City, Midrand

2090

8. REGISTRATION NUMBER(S):

NEXILOK 20: 46/11.4.3/0506

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

16 November 2021

10. DATE OF REVISION OF THE TEXT:

27 August 2025