Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FLOXIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg Norfloxacin.

Sugar Free

Contains sodium:

Each tablet contains 1,709 mg sodium

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

White special capsule shape biconvex film coated tablets with breakline on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- **FLOXIN** is indicated for the treatment of complicated and uncomplicated, upper and lower urinary tract infections including cystitis, pyelitis, cystopyelitis and pyelonephritis caused by bacteria susceptible to **FLOXIN**.
- In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly.

4.2 Posology and method of administration

Posology

Susceptibility of the causative organisms to **FLOXIN** should be tested.

Adults:

Uncomplicated lower urinary tract infections (e.g. cystitis):

- One tablet (400 mg) every twelve hours for three days.

Complicated urinary tract infections:

- One tablet (400 mg) every twelve hours for 7 to 10 days.

Children:

Use is not recommended in infants and children, since norfloxacin causes arthropathy in immature animals (See section 4.3).

Geriatrics:

No geriatric-specific problems have been demonstrated. However, elderly patients are more likely to have an age-related decrease in renal function, which may require an adjustment in dosage.

Renal impairment:

Doses may need to be reduced in renal impairment; 400 mg once daily has been suggested with creatinine clearance is 30 ml per minute (See section 4.3)

The presence of food in the stomach may slightly decrease or delay the absorption of norfloxacin. Therefore, **FLOXIN** should preferably be taken with a full glass (240 ml) of water on an empty stomach (either 1 hour before or 2 hours after meals or ingestion of milk).

Multivitamins, products containing iron or zinc, antacids containing magnesium and aluminium, sucralphate, or products containing didanosine should not be taken within 2 hours administration of **FLOXIN** (See section 4.5).

Method of administration

For oral administration

4.3 Contraindications

FLOXIN is contra-indicated:

- In patients with a known hypersensitivity to the active substance, norfloxacin or any chemically related quinolone antibacterial or to any of the excipients in listed in section 6.1.
- In patients with a creatinine clearance of less than 30ml per minute.
- With the concomitant use of angiotensin converting enzyme (ACE) inhibitors/renin-angiotensin blockers in patients with moderate to severe renal impairment.
- In children or adolescents under the age of 18 years, as experimental evidence indicates that species variable, reversible lesions of the cartilage of weight bearing joints has been seen in immature members of certain animal species.
- In pregnancy and lactation.
- In patients with moderate to severe renal impairment.
- In patients with confirmed mitral valve and /aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated.

4.4 Special warnings and precautions for use

As flouroquinolones may cause central nervous system (CNS) stimulation or toxicity, **FLOXIN** should not be used in patients with CNS disorders including cerebral arteriosclerosis, epilepsy, a history of convulsions, or known factors that predispose to seizures. Convulsions have been reported with norfloxacin, as in **FLOXIN**. (See section 4.8)

Tendinitis and/or tendon rupture, particularly affecting the Achilles tendon, may occur with **FLOXIN** (See section 4.8). Such reactions have been reported, particularly in older patients and in those treated concurrently with corticosteroids. At the first sign of pain or inflammation, patients should discontinue **FLOXIN** and rest the affected limbs. These reactions may occur even after treatment has been stopped.

Quinolones have been associated with prolongation of the QTc interval on the electrocardiogram and cases of dysrhythmia (including torsade de pointes) have been reported (See section 4.8). Caution

should be exercised when using **FLOXIN** in patients with hyperkalaemia, significant bradycardia or undergoing concurrent treatment with class Ia or class IIII antidysrhythmics.

FLOXIN should therefore be used with caution in patients taking cisapride, erythromycin, antipsychotics, tricyclic antidepressants or who have any personal or family history of QTc prolongation.

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (See section 4.5 and 4.8).

The maximum recommended dosage of 400 mg twice daily should not be exceeded and the patient should drink sufficient fluids to ensure a proper state of hydration and adequate urinary output.

Care is necessary in patients with impaired hepatic or renal function, or glucose-6-phosphate dehydrogenase deficiency. Haemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who take quinolone antibacterial agents, including **FLOXIN** (See section 4.8).

Exposure to strong sunlight or sun lamps should be avoided. Photosensitivity reactions have been observed in patients who were exposed to excessive sunlight while receiving **FLOXIN**. **FLOXIN** therapy should be discontinued if photosensitivity occurs.

Exacerbation of myasthenia gravis has been reported with **FLOXIN** and may lead to life-threatening weakness of the respiratory muscles. Caution should be exercised when using quinolones, including **FLOXIN**, in patients with myasthenia gravis (See section 4.8).

Pseudomembranous colitis has been reported with **FLOXIN** and may range in severity from mild to life-threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to administration of **FLOXIN.** A toxin produced by produced by *Clostridium difficile* is a primary cause of pseudomembranous colitis.

If *Clostridium difficile* –associated diarrhoea (CDAD) is suspected or confirmed, ongoing use not directed against *C. difficile* should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and or aortic valve regurgitation (See section 4.3).

Superinfection with organisms not susceptible to norfloxacin is possible. Such organisms include *Candida, Clostridium difficile*, and *Streptococcus pneumoniae*.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly (see section 4.2).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with **FLOXIN** (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, **FLOXIN** should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of **FLOXIN**, treatment with **FLOXIN** must not be restarted in this patient at any time.

Use in children:

FLOXIN has been reported to cause arthropathy in immature animals. The safety of **FLOXIN** in children has not been established and therefore the use of **FLOXIN** in prepubertal children or growing adolescents is contraindicated (See section 4.2 and 4.3).

FLOXIN contains:

1,709 mg sodium per tablet

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

Propylene glycol

This medicine contains 1,160 mg propylene glycol in each tablet.

4.5 Interaction with other medicines and other forms of interaction

Nitrofurantoin:

Antagonism has been demonstrated between **FLOXIN** and nitrofurantoin and they should not be prescribed together.

Urinary alkalisers:

Urinary alkalisers, such as citrates and sodium bicarbonate, may reduce solubility of **FLOXIN** in the urine. Patients should be observed for signs of crystalluria and nephrotoxicity.

Antacids and multivitamins:

Antacids, multivitamins, products containing ferrous sulphate or zinc and sucralphate may reduce the absorption of **FLOXIN** by chelation, resulting in lower serum and urine concentrations. **FLOXIN** should be taken at least 2 hours before or after any of these medicines.

Ciclosporin:

Concurrent use with ciclosporin has been reported to evaluate serum creatinine concentrations. Elevated serum levels of ciclosporins have been reported with concomitant use of **FLOXIN**. Ciclosporin serum levels should be monitored and appropriate ciclosporin dosage adjustments made when these medicines are used concomitantly.

Didanosine:

Didanosine should not be administered concurrently with or within 2 hours of the administered of **FLOXIN**, because it may interfere with absorption, resulting in lower serum and urine level **FLOXIN**.

Probenecid:

Concurrent use with probenecid decrease the renal tubular secretion of **FLOXIN**, resulting in decreased urinary excretion of **FLOXIN**, prolonged elimination half-life, and increased risk of toxicity.

Warfarin:

Concurrent use with warfarin has been reported to increase the anticoagulant effect of warfarin (by displacing significant amounts from serum albumin binding sites), increasing the chance of bleeding. When concomitant administration of warfarin and **FLOXIN** cannot be avoided, the prothrombin time (INR) should be carefully monitored in all patients.

Medicines metabolized by CYP1A2:

Quinolones, including **FLOXIN**, have been shown *in vitro* to inhibit CYP1A2. Concomitant use with medicines metabolized by CYP1A2 (e.g. caffeine, clozapine, ropinirole, theophylline) may results in increase levels of these medicines, with the potential risk of increased toxicity. Patients taking any concomitant medicines metabolized by CYP1A2 should be carefully monitored.

Specially in relation to this interaction:

- Monitoring if theophylline plasma levels should be considered and dosage of theophylline adjusted as required.
- The dose of clozapine or ropinirole may need to be adjusted in patients already taking these medicines if **FLOXIN** is introduced or withdrawn.

Glibenclamide:

The concomitant administration of quinolones, including **FLOXIN**, with glibenclamide (a sulphonylurea agent) may result in severe hypoglycaemia. Therefore, monitoring of blood glucose is recommended when these agents are co-administered (See section 4.4 and 4.8).

Non-steroidal anti-inflammatory drugs (NSAIDs):

The concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) with a quinolone, including **FLOXIN**, may increase the risk of CNS stimulation and convulsive seizures. Therefore, **FLOXIN** should be used with caution in patients receiving NSAIDs concomitantly.

Use of tizanidine and norfloxacin is contraindicated.

Norfloxacin should be used with caution in patients with cisapride, erythromycin, antipsychotics, tricyclic antidepressants, anti-arrhythmics or who have any personal or family history of QTc prolongation.

Renal tubular section of methotrexate may be inhibited by nofloxacin, potentially increasing its toxicity.

A case series of 16 reports of acute kidney injury (AKI) associated with enalapril and ciprofloxacin as co-suspect or interacting medicines was identified in VigiBase, the WHO global database of individual case safety reports. Analysis of 11 cases indicated that in most patients although clinical conditions and a number of medicines were likely to have increased their risk of AKI, including ACE inhibitor-related AKI, the event did not occur until after a ciprofloxacin prescription lending weight to ciprofloxacin being the cause or a combined action of ciprofloxacin and enalapril. Furthermore, the interaction between ACE inhibitors and fluoroquinolones to precipitate acute kidney injury is a class effect for all ACE inhibitors and not just enalapril, and also a class effect of all the fluroquinolones not just with ciprofloxacin. The publication signal April 2017 from Uppsala Monitoring Centre also indicated that with a nested control study in older men, there was a greater than additive risk to develop acute kidney injury with the concomitant use of fluoroquinolones and renin angiotensin receptor blockers. Thus, concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safe use of **FLOXIN** in pregnant women has not been established; quinolones such as norfloxacin has been reported to cause arthropathy in immature animals and therefore its use during pregnancy is contraindicated (See section 4.3).

Breastfeeding

It is not known whether **FLOXIN** is excreted in human milk; administration to mothers breastfeeding their infants is contraindicated (See section 4.3).

4.7 Effects on ability to drive and use machines

The ability to drive or operate machinery may be impaired by **FLOXIN**, especially when alcohol is also taken. **FLOXIN** may cause dizziness and light-headedness and, therefore, patients should know how they react to **FLOXIN** before they drive or operate machinery, or engage in activities requiring mental alertness and coordination.

4.8 Undesirable Effects

System Organ Class	Frequent	Less frequent	Frequency Unknown
Infections and infestations			Vaginal candidiasis
Blood and the lymphatic system disorders			eosinophilia, leucopenia, thrombocytopenia, neutropenia, agranulocytosis, haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency (see section 4.4)

Immune system disorders	Hypersensitivity reactions, including skin rash, photosensitivity, itching or redness, Stevens-Johnsons syndrome (see **"Skin and subcutaneous tissue disorders"**), shortness of breath (dyspnoea), swelling of face and neck (angioedema), vasculitis		Anaphylaxis, urticaria, arthritis, myalgia, arthralgia and interstitial nephritis (as part of a hypersensitivity reaction)
Metabolism and nutrition disorders			Hypoglycaemia, particularly in diabetic patients, Hyperglycaemia, Hypoglycaemic coma (see section 4.4 and 4.5),
Psychiatric disorders	Insomnia, nervousness.	Psychosis , depression, agitation, hallucinations, sleep disturbances, anxiety, irritability, euphoria.	

Nervous system disorders	Central nervous system toxicity (dizziness, headache, drowsiness).	Central nervous stimulation (convulsions, confusion, tremors), disorientation.	Peripheral neuropathy, including Guillian-Barré syndrome, paraesthesia, hypoaesthesia, myoclonus, dysgeusia (see section 4.4)
Eye disorders		Visual disturbances, epiphora	Peripheral neuropathy
Ear and labyrinth disorders		Tinnitus.	Hearing loss.
Cardiac disorders		Prolonged QTc interval and ventricular dysrhythmia (including torsade de pointes) (see section 4.4)	Mitral valve and/ or aortic valve regurgitation
Vascular disorders			Leukocytoclasticvasculitis (see **"Immune system disorders").**
Gastro-intestinal disorders	Cramps, anorexia, heartburn, nausea, vomiting, diarrhoea, abdominal pain and dyspepsia. Pseudomembranous colitis has been reported	Pancreatitis	Pseudomembranous colitis

Hepato-biliary disorders		Transient increases in serum creatinine or blood urea and acute renal failure secondary to interstitial nephritis; crystalluria	Hepatitis, jaundice including cholestatic jaundice, elevated liver function tests (see **"Investigations"**)
Skin and subcutaneous tissue disorders	Rash and hypersensitivity - type reactions affecting the skin	Vasculitis, Anaphylaxis has been reported, photosensitivity.	Stevens - Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme (see **"Immune system disorders"**), pruritis. DRESS (Drug reaction with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders		Reversible arthralgia and joint erosions have been documented in immature animals. ~~Tendon damage has been reported.~~ Myalgia.	Tendinitis, tendon rupture, exacerbation of myasthenia gravis (see section 4.4)
Renal and urinary disorders		Interstitial nephritis (bloody or cloudy urine, fever, rash, swelling of feet or lower legs).	Crystalluria, especially when the dosage has exceeded the recommended dosage, renal failure.

Reproductive system and breast disorders			gynaecomastia
Investigations			Abnormal laboratory values observed include elevation of ALT (SGPT), AST (SGOT), alkaline phosphatase, bilirubin, blood urea and creatinine, elevated creatine kinase (CK).

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 asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Adequate hydration must be maintained. Treatment is symptomatic and supportive. ECG monitoring should be undertaken, because of the possibility or QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.20.1.1 Broad and medium spectrum antibiotics.

ATC code: J01MA06

Pharmacotherapeutic group: Fluoroquinolones

Norfloxacin is a fluorinated 4-quinolone or fluoroquinolone antibacterial agent structurally related to nalidixic acid. Flouroquinolones are bacterial; acting intracellularly by inhibiting DNA gyrase. DNA gyrase is an essential bacterial enzyme that is a critical catalyst in the duplication, transcription and repair of bacterial DNA.

Flouroquinolones, including norfloxacin, are active against a wide range of aerobic Gram-positive and Gram-negative organisms (broad spectrum).

Mechanism(s) of resistance:

The major mechanism of resistance to quinolones, including norfloxacin, is through mutations in the genes that encode for DNA gyrase and topoisomerase IV, the targets of quinolone action.

Additional mechanisms of resistance include mutations in the cell membrane proteins, which alter membrane permeability and the developments of efflux pumps.

There is no cross-resistance between norfloxacin and structurally unrelated antibacterial agents, such as penicillins, cephalosporins, tetracyclines, macrolides, aminoglycosides and sulphonamides, 2,4-diaminopyrimidines, or combinations thereof (e.g. co-trimoxazole).

Species for which acquired resistance may be a problem:

Gram-positive aerobes:

Enterococcus faecalis

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus agalactiae

Grams-negative aerobes:

Citrobacter freudii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Providencia stuartii

Pseudomonas aeroginosa

Serratia marcescens

5.2 Pharmacokinetic properties

Absorption:

Norfloxacin is well absorbed following oral administration. At least 30 – 40 % of an oral dose of norfloxacin is absorbed. This results in a serum concentration of 1,5 ug/ml being attained approximately 1 hour after administration of a 400 mg dose. Mean serum half-life is 3 to 4 hours and is independent of dose.

Distribution:

Flouroquinolones are widely distributed to most body fluids and tissues; high concentrations are attained in the kidneys, gall bladder, liver, lungs, gynaecological tisse, prostatice tissue, phagocytic cells, urine, spectrum and bile. Flouroquinolones are primarily excreted via the renal tract.
Protein binding is less than 15 %.

Biotransformation and elimination:

Norfloxacin is eliminated through metabolism, biliary excretion and renal excretion.
Renal excretion occurs by both glomerular filtration and net tubular secretion, as evidenced by the high rate or renal clearance (approximately 275 ml/min). After a single 400 mg dose, urinary

concentrations reach a value of 200 ug/ml or more in healthy volunteers and remain above 30 ug/ml for atleast 12 hours. In the first 24 hours, 33 – 48 % of the medicines is recovered in the urine. Norfloxacin exists in the urine as norfloxacin and six active metabolites of lesser antimicrobial potency. The parent compound accounts for over 70 % of total excretion. The bacteriocidal potency of norfloxacin is not affected by the pH of urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

- Croscarmelose sodium (Ac-di-sol),
- Magnesium stearate,
- Microcrystalline cellulose,
- Purified talc,
- Sodium lauryl sulphate.

Coating

- Hydroxypropylmethyl cellulose (5 cps),
- Polyethylene glycol 400,
- Propylene glycol,
- Purified talc,
- Titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry place, at or below 25 ^{0}C.

Protect from light.

6.5 Nature and contents of container

FLOXIN is supplied in packs of 6 and 10 tablets. (Blistered)

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext. 1

Roodepoort

1724

South Africa

8. REGISTRATION NUMBERS

32/20.1.1/0377

9. DATE OF FIRST AUTHORISATION

29 May 2003

10. DATE OF REVISION OF THE TEXT

21 May 2023