Approved Professional Information for Medicines for Human Use:

AVOXA 400 mg film coated tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AVOXA Film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each AVOXA film-coated tablet contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

Contains sugar as mannitol 175,70 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Dark-pink, biconvex, oblong film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVOXA is indicated for the treatment of severe and/or complicated infections caused by moxifloxacin-sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated.

AVOXA is not indicated/ approved for the initiation of treatment (first line treatment) of

infections described as mild/ moderate/ acute and uncomplicated, caused by bacteria sensitive to moxifloxacin, unless treatment with other appropriate antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated or not tolerated.

- Respiratory tract infections:

AVOXA tablets are indicated for the treatment of the following bacterial respiratory tract infections where treatment with other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive have failed, are contraindicated or not tolerated.

- Acute exacerbations of chronic obstructive pulmonary disease (COPD) including chronic bronchitis (AECB) caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae*, methicillin-sensitive *Staphylococcus aureus* or *Moraxella catarrhalis*.
- Community acquired pneumonia (CAP) (of mild to moderate severity) caused by *Streptococcus pneumoniae* (including penicillin-resistant strains and multi-drug resistant strains*)*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Klebsiella pneumoniae,* methicillin-sensitive *Staphylococcus aureus,* or *Moraxella catarrhalis*.
- Acute bacterial sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* or *Moraxella catarrhalis*.

- Uncomplicated pelvic inflammatory disease (i.e. infections of the female upper genital tract, including salpingitis and endometritis), (not caused by *Neisseria gonorrhoea*) where these infections are compliant with the indication statement, with special reference to the second part of the statement.
- Severe and/or complicated skin and skin structure infections (including diabetic foot infections) caused by methicillin sensitive *Staphylococcus aureus, Streptococcus pyogenes*, *Enterococcus faecalis, Escherichia coli*, *Streptococcus agalactiae, Klebsiella pneumoniae, Proteus mirabilis* or *Enterobacter cloacae.*
- Severe and/or complicated intra-abdominal infections including polymicrobial infections such as

abscesses.

Appropriate culture and susceptibility tests should be performed before treatment, in order to isolate and identify organisms causing infection and to determine their susceptibility to AVOXA. Therapy with AVOXA may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and method of administration

Posology

The recommended dose for AVOXA is 400 mg once-daily for all indications.

Method of administration – Adults

The tablets are swallowed whole with a glass of water. They can be taken independent of food intake; fluid should be consumed liberally.

Duration of treatment

The duration of treatment to contain and eradicate an infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. In general, antibiotic therapy should continue for 3 to 4 days after the manifestations of the infection have cleared.

The recommended duration of treatment for the treatment of upper and lower respiratory tract infections is as follows:

Acute exacerbation of chronic obstructive pulmonary disease (COPD) including chronic bronchitis	5 days
Community acquired pneumonia	7 to 14 days*
Acute sinusitis	10 days

The recommended duration of treatment in skin and soft tissue infections is as follows:

Uncomplicated skin and skin structure infections	7 days
Complicated skin and skin structure infections	7 to 21 days*

The recommended duration[s] of treatment for other infections is as follows:

Uncomplicated pelvic inflammatory disease	14 days
Complicated intra-abdominal infections total treatment duration for sequential therapy (intravenous followed by oral therapy)	5 to 14 days*

The recommended duration of treatment for the indication being treated should not be exceeded.

*Therapy may be initial intravenous administration, followed by oral tablet administration (sequential therapy), when clinically indicated.

Special Populations

Elderly

No adjustment of dosage is required in the elderly.

Children

The use of AVOXA in children and adolescents below the age of 18 years is contraindicated.

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic insufficiency (Child Pugh A and B). No pharmacokinetic data is available for patients with severely impaired liver function (Child-Pugh C). Due to the lack of data, AVOXA is not recommended in patients with severe hepatic impairment (see section 4.3).

Renal impairment

No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance ≤ 30 mL/min/1,73m²). There is no pharmacokinetic data available in patients on dialysis treatment, or in patients with advanced renal impairment who are not on a dialysis programme. AVOXA should therefore not be used in these patients.

4.3 Contraindications

- Known hypersensitivity to AVOXA, other quinolones or any of the excipients listed in section 6.1.
- Patients with severe hepatic insufficiency (Child-Pugh C) and in patients with transaminases increase > 5 fold ULN. No dosage adjustment is required in patients with mild to moderate hepatic insufficiency (Child-Pugh A and B).
- Patients with a history of tendon, muscle, joint, nerve, central nervous system or psychiatric disorders, especially those related to previous quinolone/ fluoroquinolone use where alternative appropriate antibiotic choices are available.
- A history of convulsions, epilepsy or difficult to control epilepsy disorders.
- Congenital or documented acquired QT prolongation.
- AVOXA should not be used concurrently with other medicines that prolong the QT interval; (see section 4.5).
- Electrolyte disturbances, particularly in uncorrected hypokalaemia.
- Clinically relevant heart failure with reduced left-ventricular ejection fraction.
- Clinically relevant bradycardia.
- Previous history of symptomatic dysrhythmias.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection where alternative antibiotic choices are available.
- Concomitant use of fluoroquinolones, such as AVOXA, with ACE inhibitors/ angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤30mL/min) and in the elderly.

- Myasthenia gravis.
- Patients with confirmed mitral valve and/aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated.
- Use in pregnancy and lactation (see section 4.6).
- Patients below 18 years of age.

AVOXA is contraindicated in patients under 18 years and in growing adolescents. Reversible lesions of the cartilage of weight bearing joints in immature members of certain animal species have been reported.

4.4 Special warnings and precautions for use

THE SAFETY AND EFFECTIVENESS OF AVOXA IN PAEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED (see sections 4.3 and 4.6).

Prolongation of QTc interval and potentially QTc-prolongation-related clinical conditions

AVOXA HAS BEEN SHOWN TO PROLONG THE QTc INTERVAL ON THE ELECTROCARDIOGRAM (ECG) IN SOME PATIENTS (see section 4.3).

AVOXA SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QT INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALAEMIA AND PATIENTS RECEIVING CLASS IA (e.g. QUINIDINE, PROCAINAMIDE) OR CLASS III

(e.g. AMIODARONE, SOTALOL) ANTI-DYSRHYTHMIC MEDICINES (see section 4.3).

AVOXA should be used with caution in patients with on-going prodysrhythmic conditions (especially women and elderly patients), such as acute myocardial ischaemia or QT prolongation as this may lead to an increased risk for ventricular dysrhythmias (incl. torsade de pointes) and cardiac arrest (see section 4.3).

The magnitude of QT prolongation may increase with increasing concentrations of AVOXA. Therefore, the recommended dose should not be exceeded.

If signs of cardiac dysrhythmia occur during treatment with AVOXA, treatment should be stopped and an ECG should be performed.

Hypersensitivity / allergic reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported for AVOXA, even following a single dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Serious anaphylactic reactions require immediate emergency treatment with epinephrine (adrenaline). At the first sign of a skin rash or other signs of an allergic reaction AVOXA should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Hypersensitivity events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: rash, fever, eosinophilia, jaundice, and hepatic necrosis.

Severe liver disorders

AVOXA may be associated with a risk for potentially serious hepatic injury (including hepatic failure and fatal cases). Patients should be advised to discontinue use and contact their doctor immediately if signs and symptoms of fulminant hepatic disease develop, such as abdominal pain, loss of appetite, pale coloured stools, severe itching or rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.

Liver function tests/investigations should be performed in cases where indications of liver dysfunction occur.

Tendon inflammation and tendon rupture

Tendon inflammation and rupture may occur with quinolone therapy such as AVOXA, particularly in elderly patients and in those treated concurrently with corticosteroids. At the first sign of pain or

inflammation, patients should discontinue treatment with AVOXA, rest the affected limb(s) and consult their doctor immediately in order to initiate appropriate treatment (e.g. immobilisation) for the affected tendon. Tendon rupture may occur within 48 hours after starting treatment with AVOXA and may be bilateral. Tendon inflammation and rupture may occur even up to several months after discontinuing AVOXA.

The oral administration of moxifloxacin (as contained in AVOXA) caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage.

Antibiotic-associated diarrhoea including colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported with the use of AVOXA and may range in severity from mild diarrhoea to fatal colitis. Therefore it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of AVOXA. If AAD or AAC is suspected or confirmed, on-going treatment with AVOXA should be discontinued and adequate therapeutic measures should be initiated immediately. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission. Medicines inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

Serious bullous skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with AVOXA (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including AVOXA. In some cases depression or psychotic reactions have progressed to suicidal thoughts and self-endangering behaviour such as suicide attempts (see section 4.8). In the event that the patient

develops these reactions, AVOXA should be discontinued and appropriate measures instituted. Caution is recommended if AVOXA is to be used in psychotic patients or in patients with history of psychiatric disease.

Central nervous system disorders

AVOXA may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, and hallucinations. These reactions may occur following the first dose. If these reactions occur in patients receiving AVOXA, the medicine should be discontinued and appropriate measures instituted.

AVOXA should be used with caution in patients with known or suspected CNS disorders (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (see section 4.8). In case of seizures, treatment with AVOXA should be discontinued and appropriate measures instituted.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones such as in AVOXA. Patients under treatment with AVOXA should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see section 4.8).

Patients with myasthenia gravis

AVOXA should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated (see section 4.3).

Aortic aneurysm and dissection

There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones particularly in the elderly population.

Therefore, fluoroquinolones, such as AVOXA, should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis) (see section 4.3).
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department.

Mitral valve and/or aortic valve regurgitation

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 such as AVOXA should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see section 4.3).

Patients with renal impairment

Elderly patients with renal disorders should use AVOXA with caution if they are unable to maintain adequate fluid intake, because dehydration may increase the risk of renal failure.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see section 4.8).

Prevention of photosensitivity reactions

Quinolones such as AVOXA have been shown to cause photosensitivity reactions in patients. There was however no phototoxicity reported with AVOXA at the recommended dose. Nevertheless, patients should be advised to avoid exposure to either UV irradiation (including artificial ultraviolet light such

as tanning beds) or extensive and/or strong sunlight during treatment with AVOXA. The patient should be informed to immediately contact his/her attending physician if sunburn-like reaction or skin eruptions occur.

Patients with glucose-6-phosphate dehydrogenase deficiency

Patients with a family history of, or actual glucose-6-phosphate dehydrogenase deficiency are prone to haemolytic reactions when treated with quinolones, therefore, AVOXA should be used with caution in these patients.

Patients with pelvic inflammatory disease

For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with AVOXA is not recommended.

Pelvic inflammatory disease may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Therefore in such cases AVOXA should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Patients with MRSA infections

AVOXA, is not recommended for the treatment of MRSA (methicillin resistant *Staphylococcus aureus*) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial medicine should be started.

Paediatric population

Due to adverse effects on the cartilage in juvenile animals the use of AVOXA is contraindicated in children (see section 4.3).

Fluid intake

An adequate fluid intake should be maintained during treatment with AVOXA and excessive alkalinity of the urine avoided because of crystalluria.

Dysglycaemia

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported with AVOXA. In moxifloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving treatment concomitantly with an oral hypoglycaemic agent (e.g. sulphonylurea) or with insulin. Careful monitoring of blood glucose is recommended in diabetic patients (see section 4.8).

Interference with biological tests

Treatment with AVOXA, may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving AVOXA.

Concomitant use with ACE inhibitors/ angiotensin receptor blockers

Concomitant use of fluoroquinolones, such as AVOXA, and ACE inhibitors/ 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 concomitant treatment with fluoroquinolones and ACE inhibitors/ angiotensin receptor blockers.

Excipient mannitol

AVOXA contains mannitol and this may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Antidysrhythmic medicines

AVOXA should be avoided in patients receiving Class IA (e.g. quinidine, hydroquinidine, disopyramide, procainamide) or Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antidysrhythmic medicines. Information should be obtained from patients regarding any other medications taken concurrently with AVOXA, including over-the-counter medicines.

AVOXA may add to the QTc prolonging effects of other medicines such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants.

ACE inhibitors/ angiotensin receptor blockers

Concomitant use of fluoroquinolones, such as AVOXA, and ACE inhibitors/ angiotensin receptor blockers may precipitate acute kidney injury in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and the elderly (see section 4.3). Renal function should be assessed before initiating treatment and monitored during concomitant treatment with fluoroquinolones and ACE inhibitors/ angiotensin receptor blockers.

Histamine H_2 antagonists

Possibly due to changes caused in gastric pH if histamine H_2 antagonists are taken, these medicines may influence the pharmacokinetics of AVOXA, but do not seem to be of clinical significance.

The concomitant administration with ranitidine did not change the absorption characteristics of AVOXA significantly.

Antacids, minerals and multivitamins

Concomitant ingestion of AVOXA together with antacids, minerals and multi-vitamins may result in impaired absorption of AVOXA due to formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral medicines and other preparations containing magnesium, aluminium and other minerals such as iron should be administered at least 4 hours before or 2 hours after ingestion of an oral AVOXA dose.

Warfarin

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with AVOXA.

Infectious and inflammatory conditions, advanced age and poor general status of the patient are risk factors. International Normalised Ratio (INR) monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Digoxin

The pharmacokinetics of digoxin are significantly influenced by AVOXA. After repeated dosing in healthy volunteers AVOXA increased Cmax of digoxin by approximately 30 % at steady state without affecting AUC or trough levels. Increased clinical and laboratory monitoring of patients on digitalis therapy is advised.

Itraconazole

The pharmacokinetics of moxifloxacin are not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with AVOXA and vice versa.

Theophylline

No influence of AVOXA on theophylline pharmacokinetics (and vice versa) at steady is reported. Hence, no recommendations with respect to theophylline dosing need to be given.

Probenecid

No significant effect on apparent total body clearance and renal clearance of AVOXA, is reported. Therefore, dosing adjustments need not be made when both medicines are administered concomitantly.

Antidiabetics

Concomitant administration of AVOXA tablets with glibenclamide may result in a decrease of

approximately 21 % in the peak plasma concentrations of glibenclamide.

Oral Contraceptives

No interaction has occurred following concomitant oral administration of AVOXA with oral contraceptives.

Calcium supplements

No interaction has occurred following concomitant oral administration of with calcium supplements.

Morphine

Parenteral administration of morphine with AVOXA did not reduce the oral bioavailability of moxifloxacin.

Medicines metabolised by Cytochrome P450 enzymes

It is reported that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that AVOXA is unlikely to alter the pharmacokinetics of medicines metabolised by these enzymes (e.g. midazolam, ciclosporin, warfarin, theophylline).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Concomitant administration of a nonsteroidal anti-inflammatory drug with a quinolone may increase the risks of CNS stimulation and convulsions (see section 4.4).

Charcoal

Concomitant administration of charcoal with a dose of 400 mg oral moxifloxacin will reduce systemic availability of AVOXA by more than 80 %.

Atenolol:

The pharmacokinetics of atenolol are not significantly altered by AVOXA. Following single dose administration in healthy subjects, the AUC was marginally increased (by approximately 4 %) and peak concentrations were decreased by 10 %.

Food and dairy products

Absorption of AVOXA was not altered by food intake. Therefore, **AVOXA** can be taken with or without food.

Interference with biological tests

AVOXA may interfere with the *Mycobacterium spp*. culture test by suppression of mycobacterial growth, causing false negative results.

4.6 Fertility, pregnancy and lactation

The use of AVOXA during pregnancy and lactation is contraindicated (see section 4.3).

Pregnancy

The use of AVOXA during pregnancy is contraindicated (see section 4.3). The safe use of AVOXA in pregnancy has not been established.

Lactation

The use of AVOXA is contraindicated in lactation (see section 4.3). Mothers taking AVOXA should not breastfeed their babies as quinolones are excreted in human milk. AVOXA has been shown to cause lesions in the cartilage of the weight-bearing joints of immature animals.

4.7 Effects on ability to drive and use machines

AVOXA may cause dizziness and light-headedness; patients should know how they react AVOXA before they operate a vehicle or machinery or engage in activities requiring mental alertness or coordination.

No studies on the effects of AVOXA on the ability to drive and use machines have been performed. However, fluoroquinolones (such as AVOXA) may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (e.g. dizziness; acute, transient loss of vision) or acute and short lasting loss of consciousness (syncope).

4.8 Undesirable effects

a) Tabulated list of adverse reactions

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis		
Blood and lymphatic system disorders		Anaemia Leukopenia Neutropenia Thrombocytopenia Thrombocythemia Blood eosinophilia Prolonged prothrombin time Increased INR Increased prothrombin level	

		Abnormal/decreased INR Agranulocytosis Abnormal partial thromboplastin time (aPTT) Pancytopenia	
Immune system disorders		Allergic reaction Pruritus Rash Urticaria Anaphylactic/anaphylactoid reaction Anaphylaxis including in some cases life-threatening shock Allergic oedema / angioedema (including laryngeal oedema, potentially life-threatening	

Endocrine disorders		Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders		Hyperlipidaemia Hyperglycaemia Hyperuricaemia Hypoglycaemia Hypoglycaemic coma	
Psychiatric disorders		Anxiety reactions Psychomotor hyperactivity/ agitation Emotional lability Depression (in some cases potentially culminating in self-injurious behaviour, such as suicidal ideation/ thoughts, or suicide attempts) Hallucinations, Depersonalisation	

		Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/ thoughts, or suicide attempts)	
Nervous system disorders	Headache Dizziness .	Paraesthesia and dysaesthesia Taste disorders (incl. aguesia in some cases) Confusion and disorientation Sleep disorders (predominantly insomnia) Tremor Vertigo Somnolence Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams	Guillain- Barré Syndrome

		Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; leading to fall with injuries, especially in the elderly) Seizures incl. grand mal convulsions Disturbed attention, Speech disorders, Amnesia Peripheral neuropathy and polyneuropathy Hyperaesthesia	
Eye disorders		Visual disturbances incl. diplopia and blurred vision (especially in the course of CNS reactions) Transient loss of vision (especially in the course of CNS reactions Photophobia	

		Uveitis and bilateral acute iris transillumination	
Ear and labyrinth disorders		Tinnitus Hearing impairment incl. deafness (usually reversible).	
Cardiac disorders*	QT prolongation in patients with hypokalaemia.	QT prolongation Palpitations Tachycardia Atrial fibrillation Angina pectoris Ventricular tachydysrhythmia Syncope (i.e., acute and short lasting loss of consciousness) Unspecified dysrhythmias Torsade de Pointes Cardiac arrest	Aortic aneurysm and dissection.
Vascular disorders		Vasodilatation	

		Hypertension Hypotension Vasculitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea including asthmatic conditions.	
Gastrointestinal disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetite and food intake Constipation Dyspepsia Flatulence Gastritis Increased amylase Dysphagia Stomatitis Antibiotic-associated colitis (incl. pseudomembranous colitis in some	Clostridium difficile-associated disease (CDAD)

		cases associated with life-threatening complications)	
Hepatobiliary disorders	Increase in transaminases	Hepatic impairment (incl. LDH isozyme increase) Increased bilirubin Increased gamma-glutamyl-transferase (gGT) Increase in blood alkaline phosphatase Jaundice Hepatitis (predominantly cholestatic) Fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatality)	
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria Dry skin	

		Bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)	
Musculoskeletal, connective tissue and bone disorders		Arthralgia Myalgia Tendinitis Tendon rupture Muscle cramps Muscle twitching, Muscle weakness, Arthritis Muscle rigidity Exacerbation of symptoms of myasthenia gravis Rhabdomyolysis	

Renal and urinary disorders		Dehydration Renal impairment (including increase in BUN and creatinine) Renal failure	
General disorders and administration site conditions		Feeling unwell (predominantly asthenia or fatigue) Painful conditions (incl. pain in back, chest, pelvic and extremities) Sweating Oedema	

* Cases of mitral valve and/or aortic regurgitation were reported in patients treated with oral fluoroquinolones. AVOXA should not be prescribed to patients with mitral valve and or aortic valve regurgitation (see section 4.3).

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 professionals 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

Symptoms of overdose are expected to be the same as the side effect profile of AVOXA and may include nausea, vomiting and diarrhoea (see section 4.8).

No specific countermeasures after accidental overdosage are recommended. General symptomatic therapy should be initiated. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. The application of charcoal early during absorption may be useful to prevent excessive increase of systemic exposure to moxifloxacin in cases of oral overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones.

ATC Code: J01MA14

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Moxifloxacin is a fluoroquinolone antibacterial with a broad spectrum of bactericidal action.

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative microorganisms. *In-vitro* sensitivity may not always have been confirmed in clinical infection (see section 4.2).

The bactericidal action of moxifloxacin results from inhibition of both type II topoisomerases (DNA gyrase and topoisomerase IV) required for bacterial DNA replication, transcription, and repair. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety.

The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of medicines may be susceptible to moxifloxacin and other quinolones. There is no known cross-resistance between moxifloxacin and other classes of antimicrobials.

Cross-resistance has been observed between moxifloxacin and other fluoroquinolones against Gram-negative bacteria. Gram-positive bacteria, resistant to other fluoroquinolones may, however, still be susceptible to moxifloxacin.

Frequently resistant organisms
Aerobic Gram-positive micro-organisms *Enterococcus faecalis*
Aerobic Gram-negative micro-organisms *Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Proteus mirabilis*
Anaerobic micro-organisms *Bacteroides fragilis*
Inherently resistant organisms
Aerobic gram-negative micro-organisms *Pseudomonas aeruginosa*
Resistant organisms
Staphylococcus aureus (methicillin/ofloxacin resistant strains)

Coagulase negative Staphylococci (S. cohnii, S. epidermidis, S. haemolyticus, S. hominis, S. saprophyticus, S. simulans) methicillin-resistant strains.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely. The absolute bioavailability is about 90 % after oral administration of a 400 mg dose.
Pharmacokinetics are linear in the range of 50 to 1200 mg single oral dose and up to 600 mg once daily dosing over 10 days. Following a 400 mg oral dose, peak concentrations of 3,1 mg/L are reached within 0,5 to 4 h post administration and steady state is reached within 3 days. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3,2 and 0,6 mg/L respectively.

Distribution

Moxifloxacin is distributed to extravascular spaces; exposure to the medicine is high in terms of AUC (AUC_{norm}= 6 kg.h/L). The volume of distribution at steady state, V_{ss}, is about 2mL/kg. Peak concentrations, similar to those of plasma, may be reached in saliva. Low protein binding (approximately 45 %) and consequently high free peak concentrations > 10 x MIC are observed. Moxifloxacin is mainly bound to serum albumin.
Higher concentrations are reached in tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polyps) and inflamed lesions (cantharide blister fluid) concentrations than in plasma.
Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary/faecal pathways as unchanged medicine as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans, both are microbiologically inactive. The recovery from urine (approx. 19 % for unchanged moxifloxacin, approx. 2,5 % for M1 and approx. 14 % for M2) and faeces (approx. 25 % of unchanged moxifloxacin, approx. 36 % for M1, and no recovery for M2) totalled to approx. 96,98 % of the dose independent from the

route of administration.

Elimination

Moxifloxacin is eliminated from plasma and saliva with a mean terminal half-life of approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 m[ł]L /min. Renal clearance amounted to about 24 to 53 mL /min suggesting partial tubular reabsorption of the medicine from the kidneys. Approximately 19 % of the dose is excreted unchanged into the urine and approximately 25 % in the faeces. Approximately 2,5 % is recovered as M1 in the urine and 36 % in the faeces, respectively. About 14 % is recovered as M2 in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients

Croscarmellose sodium, isopropyl alcohol, magnesium stearate, mannitol, microcrystalline cellulose, povidone.

Film coating:

Opadry Pink (iron oxide red, iron oxide yellow, lecithin, polyvinyl alcohol, talc, titanium dioxide, xanthan gum).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in the original packaging at or below 25°C.

Keep blisters in the carton until required for use. Protect from moisture.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Packs containing blister strips with 5, 7 and 10 tablets, packed in clear, transparent PVC/PVDC foil sealed with silver aluminium foil, in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd

52 Mineral Crescent

Crown Extension 3

Johannesburg, 2092

South Africa

8. REGISTRATION NUMBER

46/20.1.1/0643

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 25/03/2019

10. DATE OF REVISION OF THE TEXT

29 April 2022