Approved Professional Information for Medicines for Human Use:

OFLOXACIN 200/400 mg tablets AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OFLOXACIN 200 mg tablets AUSTELL

OFLOXACIN 400 mg tablets AUSTELL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OFLOXACIN 200 mg tablets AUSTELL

Each film-coated tablet contains 200 mg ofloxacin.

OFLOXACIN 400 mg tablets AUSTELL

Each film-coated tablet contains 400 mg ofloxacin.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

OFLOXACIN 200 mg tablets AUSTELL

White, capsule shaped, biconvex, film coated tablets, scored on both sides.

OFLOXACIN 400 mg tablets AUSTELL

White, capsule shaped, biconvex, film coated tablets, scored on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OFLOXACIN AUSTELL is indicated for the treatment of the following bacterial infections, if these are due to ofloxacin-sensitive pathogens where other antimicrobials are considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated:

- Mild to moderate lower respiratory tract infections caused by *Haemophilus influenzae, Haemophilus parainfluenzae, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis* and *Pseudomonas aeruginosa.*
- Infections of the urinary tract.
- Sexually transmitted diseases: Acute uncomplicated urethral and cervical gonorrhoea, urethritis and cervicitis to *Chlamydia trachomatis*. Mixed infections of the urethra and cervix due to *Chlamydia trachomatis* and *Neisseria gonorrhoea*.
- Prevention of colonisation by gram negative organisms as part of a multi-antimicrobial regimen in patients with neutropenia, secondary to cytostatic therapy.
- In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

4.2 Posology and method of administration

OFLOXACIN AUSTELL tablets should be swallowed whole with a little liquid. It may be taken on an empty stomach or with meals. The course should be completed. If the treatment has been initiated via I.V route, it is usually possible to switch to oral route at the same dosage after a few days, when the patients' condition improves.

The dosage should be determined according to the sensitivity of the causative organism and the severity of the infection.

The following dosages are recommended:

Uncomplicated cystitis:

100 mg twice daily for 3 – 7 days.

Pyelonephritis:

200 mg twice daily for 5 – 7 days.

Infections of the lower respiratory tract:

400 mg twice daily for 7 – 10 days. The daily dose may be altered depending on the severity of the infection.

Uncomplicated urethral and cervical gonorrhoea:

A single dose of 400 mg.

Urethritis and cervicitis due to Chlamydia trachomatis:

600 mg daily in divided doses for up to 7 days.

Prevention of infections in patients with neutropenia:

400 to 600 mg daily in divided doses.

It may be necessary to increase the dose to 600 mg or 800 mg OFLOXACIN AUSTELL daily in the presence of pathogens of varying sensitivity, in severe infections.

Special populations

Renal impairment

For patients with impaired renal function and elderly patients the dosage of OFLOXACIN AUSTELL should be adjusted according to the degree of impairment. With a creatinine clearance of less than 50 mL/min to 20 mL/min, a normal single dose should be administered every 24 hours, e.g. 200 mg once daily. With a creatinine clearance of less than 20 mL/min, the normal single dose should be given initially. This dose should then be reduced to half and administered every 24 hours, e.g. 200 mg initially, thereafter 100 mg once daily.

Dosage in patients with impaired liver function

The excretion of OFLOXACIN AUSTELL may be reduced in patients with severe liver function disorders (e.g. cirrhosis of the liver with ascites). A maximum daily dose of 400 mg OFLOXACIN AUSTELL should therefore not be exceeded.

4.3 Contraindications

- Hypersensitivity to ofloxacin or related chemotherapeutic medicines of the quinolone-

derivative group, or any of the excipients listed in section 6.1.

- OFLOXACIN AUSTELL should not be administered to pregnant or lactating women.
- OFLOXACIN AUSTELL should not be administered to patients with cerebral convulsive disorders.
- OFLOXACIN AUSTELL is contraindicated in epileptics. OFLOXACIN AUSTELL should not be used in patients with pre-existing central nervous system (CNS) lesions involving a lowered convulsant threshold, e.g. after cerebrocranial injuries, inflammations in the region of the CNS, or stroke.
- OFLOXACIN AUSTELL should not be given to patients under 18 years of age.
- In patients with a history of tendon, disorders related to fluoroquinolone administration.
- Use of OFLOXACIN AUSTELL is contraindicated 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.
- Concomitant use of fluoroquinolones, such OFLOXACIN AUSTELL**,** with angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment and the elderly.

4.4 Special warnings and precautions for use

OFLOXACIN AUSTELL may alter reactivity to such an extent that the ability to drive vehicles or operate machinery may be impaired (see section 4.7).

Animal studies have shown that OFLOXACIN AUSTELL may affect joint development in immature animals.

Clostridium difficile - associated disease.

- Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment with OFLOXACIN AUSTELL or with various other antibiotics, but especially broad-spectrum antibiotics, may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis.

- If a diagnosis of pseudomembranous colitis is suspected, OFLOXACIN AUSTELL should be stopped immediately and appropriate specified antibiotic therapy should be started without delay (e.g. vancomycin or metronidazole).

Tendinitis observed may occasionally lead to rupture, involving more particularly the Achilles tendon, and occurring especially in elderly patients. Rupture seems to be favoured by treatment with corticosteroids. The onset of signs of tendinitis requires to stop the treatment, to rest both Achilles tendons by appropriate immobilisation or special heel pieces, and to take orthopaedic advice. Caution is advised when prescribing for the elderly, patients with renal impairment, patients with solid organ transplants, and those concurrently treated with corticosteroids, as the risk of fluoroquinolone-induced tendinitis and tendon rupture may be exacerbated in these patients.

OFLOXACIN AUSTELL may aggravate myasthenia gravis.

OFLOXACIN AUSTELL may inhibit the growth of *Mycobacterium tuberculosis*, giving false-negative results, in the bacteriological diagnosis of tuberculosis.

The serum concentration of OFLOXACIN AUSTELL should be monitored in patients with severe renal impairment and haemodialysis patients.

Although this has not been reported, the possibility cannot be ruled out that OFLOXACIN AUSTELL may trigger an attack of porphyria in predisposed patients.

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

Concomitant use of fluoroquinolones, such as OFLOXACIN AUSTELL**,** with ACE inhibitors/angiotensin receptor blockers (ARBs) 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 initiation of treatment and monitored during treatment with fluoroquinolones and ACE inhibitors/angiotensin receptor blockers (see section 4.3).

There is some evidence of an increased risk of aortic aneurysm and/or dissection after intake of fluoroquinolones, particularly in the elderly population. Fluoroquinolones, such as OFLOXACIN AUSTELL should only be used in patients at risk if no other treatment options are available (see section 4.3). Patients at risk are patients with a positive family history of aneurysmal disease, pre-existing aortic disease and/or dissection or other risk factors or conditions predisposing to aortic aneurysm and dissection e.g. Marfan syndrome, Vascular Ehlers Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension and known atherosclerosis. In case of sudden abdominal, chest or back pain, patients should be advised to immediately go to their medical practitioner or a hospital emergency department.

4.5 Interaction with other medicines and other forms of interaction

Antacids containing aluminium, including sucralfate, and magnesium hydroxides, aluminium phosphate or calcium, zinc, iron are liable to reduce the absorption of OFLOXACIN AUSTELL. In such cases, OFLOXACIN AUSTELL should be taken about 2 hours before taking such preparations.

There are indications of a pronounced lowering of the cerebral seizure threshold when OFLOXACIN AUSTELL are given concurrently with other medicines that lower the seizure threshold, e.g. theophylline.

The possibility cannot be ruled out that during treatment with OFLOXACIN AUSTELL, the effect of warfarin may be intensified. Patients undergoing concomitant treatment with warfarin should therefore be monitored carefully.

Excessive rises or falls in blood-sugar level may occur especially in patients with diabetes mellitus. OFLOXACIN AUSTELL may cause a slight increase in serum concentrations of glibenclamide if administered concurrently, it is therefore recommended that patients treated concomitantly with OFLOXACIN AUSTELL and glibenclamide be monitored particularly closely.

Particularly in case of high dose therapy, mutual impairment of excretion and an increase in serum levels must be considered when OFLOXACIN AUSTELL are administered together with other medicines that also undergo renal tubular secretion (such as probenecid, cimetidine, furosemide or methotrexate).

Concomitant use of fluoroquinolones, such as OFLOXACIN AUSTELL and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

4.6 Fertility, pregnancy and lactation

Safety of OFLOXACIN AUSTELL in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

OFLOXACIN AUSTELL may alter reactivity to such an extent that the ability to drive and use machines may be impaired.

4.8 Undesirable effects

The frequency of adverse reactions reported with OFLOXACIN AUSTELL are summarised in Table 1 below by system organ class (in MedDRA) and by frequency.

Post marketing adverse reactions are reported in Table 2 below.

System Organ Class	**Table 1: Tabulated list of adverse reactions**		
	Frequent	**Less frequent**	**Not known**
Infections and infestations		Enhanced development of resistant microorganisms/ pathogen resistance Fungal infection	
Blood and lymphatic System disorders		Anaemia Haemolytic anaemia Leukopenia Neutropenia Pancytopenia Eosinophilia Thrombocytopenia	Agranulocytosis Bone marrow depression
Immune system disorders		Anaphylactic reactions which may manifest as hypotension, burning sensation in the eyes, tickling cough and nasal catarrh, swelling of the skin and	

		mucous membranes involving the face, tongue and larynx, respiratory distress or circulatory collapse	
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia in diabetics treated with hypoglycaemic medicines Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders		Agitation Restlessness Sleep disorder Insomnia Psychotic disorder (for e.g. hallucination) Anxiety Confusion Nightmares Depression	Psychotic disorder and depression with self-endangering behaviour including suicidal ideation or suicide attempt Nervousness
Nervous system disorders		Dizziness	Tremor

		Headache Weakness Insomnia Nightmares Drowsiness Somnolence Paraesthesia Dysgeusia Parosmia Extrapyramidal symptoms, unsteady gait or tremor or other disorders of muscular coordination Disturbances of the senses of taste and smell	Dyskinesia Ageusia Syncope Benign intracranial hypertension (Pseudotumor cerebri)
Eye disorders		Eye irritation Visual disturbance (blurred vision) Double vision	Uveitis

		Abnormal colour vision	
Ear and labyrinth disorders		Vertigo Tinnitus Hearing loss	Impaired hearing
Cardiac disorders		Tachycardia	Ventricular dysrhythmias Torsades de pointes (reported predominantly in patients with risk factors for QT prolongation) ECG QT prolonged
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders		Cough Nasopharyngitis Dyspnoea Bronchospasm	Allergic pneumonitis Severe dyspnoea
Gastrointestinal disorders		Abdominal pain Diarrhoea Nausea	Dyspepsia Flatulence Constipation

		Vomiting Loss of appetite Enterocolitis, sometimes haemorrhagic Cholestatic jaundice	Pancreatitis
Hepatobiliary disorders		Increased hepatic enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) Increased blood bilirubin Hepatitis	Severe liver injury, including cases of acute liver failure, sometimes fatal, have been reported with ofloxacin, primarily in patients with underlying liver disorders
Skin and subcutaneous tissue disorders		Hypersensitivity reactions Pruritus Urticaria Photosensitivity Hot flushes Hyperhidrosis Pustular rash Erythema multiforme	Stevens-Johnson syndrome Acute generalised exanthemous pustulosis Rash Stomatitis Exfoliative dermatitis

		Toxic epidermal necrolysis Drug eruption Vascular purpura Systemic necrotising angiitis Petechiae, Haemorrhaghic bullae Papules Vasculitis, which can lead in exceptional cases to skin necrosis	
Musculoskeletal and connective tissue disorders		Tendonitis Arthralgia Myalgia Inflammation and tendon rupture (e.g. Achilles tendon) which may occur within 48 hours of treatment start and may be bilateral	Rhabdomyolysis and/or Myopathy Muscular weakness Muscle tear Muscle rupture Ligament rupture Arthritis
Renal and urinary		Crystalluria	Acute interstitial nephritis

disorders		Increase in serum creatinine Acute renal failure	
Congenital and familial/genetic disorders			Attacks of porphyria in patients with porphyria
General disorders and administration site conditions			Asthenia Pyrexia Pain (including pain in the back, chest and extremities)

System Organ Class	**Table 2: Post-marketing tabulated list of adverse reactions**		
	Frequent	**Less frequent**	**Not known**
Immune system disorders		Anaphylactic reaction Angioedema Anaphylactic shock	
Nervous system disorders		Peripheral sensory neuropathy	

		Convulsion	
Eye disorders		Eye irritation Visual disturbance	Uveitis
Ear and labyrinth disorders		Vertigo Tinnitus Hearing loss	Impaired hearing
Gastrointestinal disorders		Pseudomembranous colitis	
Hepatobiliary disorders			Hepatitis, which may be severe
Skin and subcutaneous tissue disorders		Photosensitivity	

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

The most important signs to be expected following acute overdosage are CNS symptoms such as confusion, dizziness, impairment of consciousness and seizures, as well as gastrointestinal reactions such as nausea and mucosal erosions.

In the event of overdose, gastric lavage and symptomatic treatment should be implemented. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 20.1.1 – Medium and broad spectrum antibiotics.

Pharmacotherapeutic group: Quinolone antibacterials, Fluoroquinolones.

ATC code J01MA01.

Ofloxacin is a fluoroquinolone antibacterial which has a broad spectrum of activity against both gram-positive and gram-negative bacteria.

Ofloxacin exerts its effect by inhibiting the bacterial DNA gyrase, which is responsible for coiling the genetic material as a prerequisite for bacterial multiplication.

The mode of action, range of activities, duration of action and MIC levels have been established mainly by means of *in vitro* studies using bacterial isolates.

5.2 Pharmacokinetic properties

Ofloxacin is well absorbed from the gastro-intestinal tract. Peak plasma concentration of 3 to 4 µg per mL is achieved 1 to 2 hours after a dose of 400 mg by mouth. The plasma half-life ranges from 6 to 8 hours; in renal impairment values of 15 to 60 hours have been reported.

About 9,4 % is bound to plasma proteins. Ofloxacin has a bactericidal effect. *In vitro* tests who that strains in which the sensitivity varies include pneumococci and uraplasma urealyticum.

Strains that are normally resistant are:

Peptococcus, Peptostreptococcus, Eubacterium spp., Fusobacterium spp. and *Treponema pallidum*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hydroxypropyl cellulose,

Magnesium stearate,

Microcrystalline cellulose,

Purified water,

Sodium starch glycollate (type-a),

Tablet coating:

Opadry -1-7000-White (Hypromellose 2910, Macrogol 400, Titanium dioxide)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C in a dry place. Protect from light.

Blisters must not be removed from the carton, until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

OFLOXACIN 200 mg AUSTELL are packed in clear PVC/PVDC-Aluminium foil blister packs containing 6 or 10 tablets, in a blue outer cardboard carton.

OFLOXACIN 400 mg AUSTELL are packed in clear PVC/PVDC-Aluminium foil blister packs containing 10 tablets in a darker blue outer cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

OFLOXACIN 200 mg AUSTELL: A39/20.1.1/0149

OFLOXACIN 400 mg AUSTELL: A39/20.1.1/0150

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 July 2006

10. DATE OF REVISION OF THE TEXT

15 November 2022