Professional Information

AUSTELL-CIPROFLOXACIN 250/500/750 mg Tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AUSTELL-CIPROFLOXACIN 250 mg film-coated tablets.

AUSTELL-CIPROFLOXACIN 500 mg film-coated tablets.

AUSTELL-CIPROFLOXACIN 750 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AUSTELL-CIPROFLOXACIN 250 mg tablets:

Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to ciprofloxacin 250 mg.

AUSTELL-CIPROFLOXACIN 500 mg tablets:

Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to ciprofloxacin 500 mg.

AUSTELL-CIPROFLOXACIN 750 mg tablets:

Each film-coated tablet contains ciprofloxacin hydrochloride equivalent to ciprofloxacin 750 mg.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

AUSTELL–CIPROFLOXACIN 250 mg:

White to creamish white, circular biconvex film-coated tablets with ‘CPR 250’ embossed on one side and `BL’ embossed on other side.

AUSTELL–CIPROFLOXACIN 500 mg:

White to creamish white, capsule shaped biconvex film-coated tablets marked ‘BL’ on one side and ‘CPR 500’ on the other side.

AUSTELL–CIPROFLOXACIN 750 mg:

White to creamish white capsule shaped film-coated tablets with ‘CPR 750’ embossed on one side and ‘BL’ embossed on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUSTELL-CIPROFLOXACIN is indicated for the treatment of severe and/or complicated infections caused by ciprofloxacin 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.

AUSTELL-CIPROFLOXACIN 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 ofloxacin, 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.

AUSTELL-CIPROFLOXACIN tablets are indicated for the treatment of the following bacterial infections, where these infections are compliant with the indication context:

Severe and/or complicated lower respiratory tract infections caused by:

Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa.*

Severe and/or complicated urinary tract infections caused by:

Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Providencia rettgeri, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus epidermidis, Streptococcus faecalis.*

Severe and/or complicated skin and soft tissue infections caused by:

Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella pnuemoniae, Morgenella morganii, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes.*

Severe and/or complicated gastro-intestinal infections:

Infective diarrhoea caused by *Campylobacter jejuni, Eschericia coli, Shigella flexneri and Shigella sonnei.*

Severe and/or complicated bone infections:

Osteomyelitis due to susceptible Gram-negative organisms.

*In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly**.**

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 AUSTELL-CIPROFLOXACIN. Therapy with AUSTELL-CIPROFLOXACIN 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 dosage range is 250 – 750 mg twice daily. The duration of treatment to contain and eradicate infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. Use the lowest effective dose for the shortest time to contain and eradicate the infection.

Severe and/or complicated infections of the lower respiratory tract:

750 mg twice daily. In cystic fibrosis patients the dose is 750 mg twice daily. The low body mass of these patients should, however, be taken into consideration when determining dosage

(7,5 to 15 mg/kg/day)

Severe and/or complicated infections of the urinary tract:

500 mg twice daily.

Severe and/or complicated infections of the skin:

750 mg twice daily.

Severe and/or complicated infections diarrhoea:

500 mg twice daily.

Severe and/or complicated bone infections:

750 mg twice daily.

Treatment may be required for 4 - 6 weeks or longer.

Special populations

Elderly

Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Impaired renal or liver function

In patients with reduced renal function, the half-life of AUSTELL-CIPROFLOXACIN is prolonged and the dosage needs to be adjusted.

For patients with changing renal function or patients with renal impairment and hepatic insufficiency, monitoring of drug serum levels provides the most reliable basis for dose adjustment.

Dose adjustment of ciprofloxacin for patients with kidney and/or liver insufficiency.

1. Kidney insufficiency:

1.1 CL_{cr} ≥ 31 mL/min/1,73m^2 ≤ 60 mL min/1,73m^2

Max 1000 mg/day orally.

1.2 CL_{cr} ≤ 30 mL/min/1,73m^2

Max 500 mg/day orally.

1.3 Impaired renal function and haemodialysis

As in 1.2 above; on dialysis days after dialysis

2. Impaired renal function and CAPD (chronic ambulatory peritoneal dialysis)

2.1 Oral administration of either ciprofloxacin film coated tablet as 500 mg tablet or 2 x 250 mg tablets is indicated

2.2 For CAPD patients with peritonitis, the recommended daily oral dose is 500 mg 4 times a day

3. Liver function disturbances: No dose adjustment

4. Liver and kidney insufficiency: As in 1.1 and 1.2 above

Method of administration

AUSTELL-CIPROFLOXACIN tablets should be swallowed whole with plenty of liquid and may be taken with or without meals.

Children and adolescents

AUSTELL-CIPROFLOXACIN is contraindicated in children less than 18 years (see sections 4.3 and 4.4).

4.3 Contraindications

- AUSTELL-CIPROFLOXACIN tablets are contraindicated in patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or to any of the inactive ingredients in AUSTELL-CIPROFLOXACIN (see section 6.1).
- Pregnancy and lactation (see section 4.6).

AUSTELL-CIPROFLOXACIN tablets are contraindicated in children under the age of 18 years. Experimental evidence indicates lesions of the cartilage of weight-bearing joints in immature members of certain animal species.

- Concomitant use of ciprofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to prolonged QTcF interval known to be associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with concomitant use at time intervals shorter than QT intervals usually associated with dysrhythmias.
- A history of tendon, muscle, joint, nerve, central nervous system, epilepsy or psychotic disorders especially those related to previous quinolone/fluoroquinolone use where alternative, appropriate antibiotic choices are available for treatment. (see section 4.4).
- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients (see section 4.4).
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available (see section 4.4).
- Concomitant use of fluoroquinolones with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) in patients with moderate to severe renal impairment and in the elderly (see section 4.4 and 4.5).
- AUSTELL-CIPROFLOXACIN is contraindicated in patients with mitral valve and/or aortic valve regurgitation, unless no safer alternative antibiotic is available, has failed or is not well tolerated. A thorough cardiovascular examination, including an echocardiogram (ECG), should be performed before AUSTELL-CIPROFLOXACIN is prescribed.

4.4 Special warnings and precautions for use

Severe infections and infections due to Gram positive or anaerobic bacteria:

AUSTELL-CIPROFLOXACIN should not be used in staphylococcal infections and infections involving anaerobic bacteria.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly (see section 4.1).

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, AUSTELL-CIPROFLOXACIN should be discontinued and adequate medical treatment is required.

Cardiac disorders

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, should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or 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). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department.

QT interval prolongation

- AUSTELL-CIPROFLOXACIN has been associated with QT prolongation (see section 4.3 and 4.8).
- Concomitant use of AUSTELL-CIPROFLOXACIN with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or

symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrhythmias (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.5) or congenital long QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia) and cardiac disease such as heart failure, myocardial infarction or bradycardia.

- A pre-treatment ECG and frequent follow up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated.
- 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 AUSTELL-CIPROFLOXACIN 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.

Concomitant use with ACE inhibitors/angiotensin receptor blockers (ARBs)

Concomitant use of fluoroquinolones, such as AUSTELL-CIPROFLOXACIN**,** 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.

Children and adolescents

AUSTELL-CIPRFLOXACIN is contraindicated in children less than 18 years (see section 4.3).

Musculoskeletal system

Myasthenia gravis

The use of AUSTELL-CIPROFLOXACIN in patients with myasthenia gravis is contraindicated if appropriate antibiotic choices are available (see section 4.3). AUSTELL-CIPROFLOXACIN may exacerbate the symptoms of myasthenia gravis.

Tendinitis and tendon rupture

AUSTELL-CIPROFLOXACIN should not be used in patients with a history of tendon disorders, especially those related to previous exposure to quinolone or fluoroquinolone use (see section 4.3).

Central Nervous System (CNS)

AUSTELL-CIPROFLOXACIN should only be used where alternative appropriate therapies have failed are contraindicated or not tolerated, since these patients are endangered due to possible central nervous system side effects. Cases of status epilepticus/seizures have been reported (see section 4.3 and 4.8).

Psychiatric effects

Psychiatric reactions may occur even after first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, AUSTELL-CIPROFLOXACIN should be discontinued.

Influence on laboratory parameters/urinary sediment

Hypoglycaemia is one of the manifestations that may occur with taking AUSTELL-CIPROFLOXACIN.

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

AUSTELL-CIPROFLOXACIN monotherapy is not suited for treatment of severe infections and infections that might be due to Gram positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)

AUSTELL-CIPROFLOXACIN is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections

Gonococcal uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone resistant *Neisseria gonorrhoeae* isolates.

Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin resistant

Neisseria gonorrhoeae can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections

Crystalluria related to the use of AUSTELL-CIPROFLOXACIN tablets has been observed. Patients receiving AUSTELL-CIPROFLOXACIN tablets should be well hydrated and excessive alkalinity of the urine should be avoided.

Resistance to fluoroquinolones of *Escherichia coli* ‑ the most common pathogen involved in urinary tract infections, varies. Prescribers are advised to take into account prevalence of resistance in *Escherichia coli* to fluoroquinolones.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections

There are limited data on the efficacy of AUSTELL-CIPROFLOXACIN in the treatment of post-surgical intra-abdominal infections.

Infections of the bones and joints

AUSTELL-CIPROFLOXACIN should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Complicated urinary tract infections and pyelonephritis

AUSTELL-CIPROFLOXACIN treatment of urinary tract infections should be considered when other treatments cannot be used and should be based on the results of the microbiological documentation.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. AUSTELL-CIPROFLOXACIN should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

AUSTELL-CIPROFLOXACIN should generally not be used in patients with a history of tendon disease/disorder related to quinolone

treatment.

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment (see section 4.8). The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment,

patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation), the treatment with AUSTELL-CIPROFLOXACIN should be discontinued

and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g.immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Patients with myasthenia gravis

AUSTELL-CIPROFLOXACIN should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated (see section 4.8).

Vision disorders

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

Photosensitivity

AUSTELL-CIPROFLOXACIN has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Seizures

AUSTELL-CIPROFLOXACIN like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with AUSTELL-CIPROFLOXACIN should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in elderly diabetic patients, receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Gastrointestinal System

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, AUSTELL-CIPROFLOXACIN should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system

Crystalluria related to the use of AUSTELL-CIPROFLOXACIN has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since AUSTELL-CIPROFLOXACIN is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with AUSTELL-CIPROFLOXACIN (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. AUSTELL-CIPROFLOXACIN should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance

During or following a course of treatment with AUSTELL-CIPROFLOXACIN, bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these medicines

concomitantly with AUSTELL-CIPROFLOXACIN should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5). Co-administration of AUSTELL-CIPROFLOXACIN and tizanidine is contraindicated.

Methotrexate

The concomitant use of AUSTELL-CIPROFLOXACIN with methotrexate is not recommended (see section 4.5).

Interaction with tests

The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking AUSTELL-CIPROFLOXACIN.

4.5 Interaction with other medicines and other forms of interaction

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

Effects of other products on ciprofloxacin:

Drugs known to prolong QT interval

AUSTELL-CIPROFLOXACIN, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin.

Consequently, AUSTELL-CIPROFLOXACIN should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and AUSTELL-CIPROFLOXACIN increases ciprofloxacin serum concentrations.

Metoclopramide

Metoclopramide accelerates the absorption of AUSTELL-CIPROFLOXACIN resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of C_{max} and AUC of AUSTELL-CIPROFLOXACIN.

Effects of AUSTELL-CIPROFLOXACIN on other medicinal products:

Tizanidine

Tizanidine must not be administered together with AUSTELL-CIPROFLOXACIN (see section 4.3).

Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of AUSTELL-CIPROFLOXACIN, potentially

leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of AUSTELL-CIPROFLOXACIN and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

On concurrent administration of AUSTELL-CIPROFLOXACIN and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin

Simultaneous administration of AUSTELL-CIPROFLOXACIN and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Cyclosporin

A transient rise in the concentration of serum creatinine was observed when AUSTELL-CIPROFLOXACIN and cyclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists

Simultaneous administration of AUSTELL-CIPROFLOXACIN with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of AUSTELL-CIPROFLOXACIN to the increase in INR (international normalised ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of AUSTELL-CIPROFLOXACIN with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Duloxetine

It was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no data are available on a possible interaction with AUSTELL-CIPROFLOXACIN, similar effects can be expected upon concomitant administration (see section 4.4).

Ropinirole

Concomitant use of ropinirole with AUSTELL-CIPROFLOXACIN, results in an increase of Cmax and AUC of ropinirole by 60 % and 84 %, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after coadministration with AUSTELL-CIPROFLOXACIN (see section 4.4).

Lidocaine

The concomitant use of lidocaine containing medicinal products with AUSTELL-CIPROFLOXACIN, reduces clearance of intravenous lidocaine by 22 %. Although lidocaine treatment was well tolerated, a possible interaction with AUSTELL-CIPROFLOXACIN associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg AUSTELL-CIPROFLOXACIN with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with AUSTELL-CIPROFLOXACIN are advised (see section 4.4).

Sildenafil

Cmax and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg AUSTELL-CIPROFLOXACIN. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Zolpidem

Co-administration of AUSTELL-CIPROFLOXACIN may increase blood levels of zolpidem. Concurrent use is not recommended.

Effects of other medicines and products on ciprofloxacin

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing medicines and mineral supplements (e.g. calcium, magnesium, aluminium, iron, zinc), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered medicines (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, AUSTELL-CIPROFLOXACIN should be administered either 1 – 2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified

orange juice) with AUSTELL-CIPROFLOXACIN should be avoided because absorption of ciprofloxacin may be reduced.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3).

Mothers taking or receiving AUSTELL-CIPROFLOXACIN should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, AUSTELL-CIPROFLOXACIN may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed with the use of AUSTELL-CIPROFLOXACIN.

The most frequently reported adverse drug reactions (ADRs) are nausea and diarrhoea.

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known**
Infections and Infestations		Mycotic superinfections	
Blood and lymphatic system disorders		Eosinophilia Leukopenia Leucocytopenia Granulocytopenia Anaemia Neutropenia Leukocytosis	

		Thrombocytopenia Thrombocytaemia Thrombocytosis Haemolytic anaemia Agranulocytosis Pancytopenia (life threatening) Bone marrow depression (life threatening) Altered prothrombin values	
Immune system disorders		Allergic reaction Allergic oedema / angiooedema Anaphylactic reaction (e.g. facial, cascular and laryngeal oedema) Anaphylactic shock (life-threatening) Serum sickness like reaction	

Endocrine disorders			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders*		Decreased appetite Hyperglycaemia Hypoglycaemia	Hypoglycaemic coma
Psychiatric disorders*		Psychomotor hyperactivity / agitation Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) Hallucinations	Mania, incl. hypomania

		Psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide)	
Nervous system disorders*		Headache Dizziness Sleep disorders/Insomnia Taste disorders Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders	Peripheral neuropathy and polyneuropathy (see section 4.4)

		Intracranial hypertension and pseudotumor cerebri Tiredness Nervousness Peripheral paralgesia Sweating Hallucinations	
Eye disorders*		Visual disturbances (e.g. diplopia) Visual colour distortions	
Ear and labyrinth disorders*		Tinnitus Hearing loss / Impaired hearing	
Cardiac disorders		Tachycardia Ventricular dysrhythmia and torsades de pointes (reported predominantly in	

		patients with risk factors for QT prolongation), ECG QT prolonged	
Vascular disorders*		Vasodilatation Hypotension Syncope Vasculitis	
Respiratory, thoracic and mediastinal disorders		Dyspnoea (including asthmatic condition)	
Gastrointestinal disorders	Nausea Diarrhoea The development of severe diarrhoea may indicate	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence	

	pseudomembranous colitis, requiring immediate treatment. In such cases AUSTELL-CIPROFLOXACIN tablets must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally 4 x 250 mg/day)	Antibiotic associated colitis (very rarely with possible fatal outcome) Pancreatitis	
Hepatobiliary disorders		Increase in transaminases Increased bilirubin Hepatic impairment Cholestatic icterus	

		Hepatitis Liver necrosis (very rarely progressing to life threatening hepatic failure)	
Skin and subcutaneous tissue disorders		Rash Pruritus Urticaria Photosensitivity reactions (blisters, sensation of skin burning) Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life threatening) Toxic epidermal necrolysis (potentially life threatening)	Acute Generalised Exanthematous Pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Musculoskeletal and connective tissue disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia Myalgia Arthritis Increased muscle tone and cramping Muscular weakness Tendinitis/Achillotenditis (e.g. painful swelling), discontinue use of AUSTELL-CIPROFLOXACIN Tendon rupture (predominantly Achilles tendon) Tendosynovitis Exacerbation of symptoms of myasthenia gravis	

Renal and urinary disorders		Renal impairment Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General disorders and administration site conditions		Asthenia Fever Oedema Sweating (hyperhidrosis) Impaired taste and smell, hyperglycaemia. Long term or repeated use of AUSTELL-CIPROFLOXACIN can lead to superinfections with resistant bacteria or fungi	

Investigations		Increase in blood Alkaline phosphatase Increased amylase Increase in transaminases or cholestatic jaundice (especially in patients with liver damage, temporary increase in urea, creatinine or hypebilirubinaemia)	International normalised ratio increased (in patients treated with Vitamin K antagonists)

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

Paediatric population

The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur frequently (see section 4.4).

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

In the event of oral overdosage, reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of AUSTELL-CIPROFLOXACIN tablets.

Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones.

ATC code J01MA02.

Mechanism of action

Ciprofloxacin is a synthetic fluoroquinolone antibiotic with *in vitro* bactericidal activity against the following Gram-negative and Gram-positive organisms and acts by inhibiting the A subunit of DNA-gyrase which is essential in the reproduction of bacterial DNA. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy.

The following organisms show varying degrees of *in vitro* sensitivity to ciprofloxacin:

Alcaligenes, Enterococcus faecalis, Flavobacterium, Gardnerella, Legionella, Mycobacterium fortuitum, Mycobacterium tuberculosis, Mycoplasma hominis, Streptococcus agalactiae, Chlamydia.

Micro-organisms resistant to ciprofloxacin:

Enterococcus faecium, Nocardia asteroids, Ureaplasma urealyticum,.

With a few exceptions anaerobes are moderately sensitive (e.g. *Peptococcus species, Peptostreptococcus species*) to resistant (e.g. *Bacteriodes, Treponema pallidum*).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, ciprofloxacin plasma levels are dose-related and peak at concentrations 1 - 2 hours later. The absolute bioavailability is approximately 70 – 80 %.

Distribution

Protein binding is low (20 – 30 %). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2 – 3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Forty to fifty percent is excreted in urine as unchanged ciprofloxacin. 20 -35 % of the dose is excreted in the faeces in 5 days. Approximately 15 % of a single dose is eliminated as metabolites. Elimination is primarily renal and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 mL/minute. The elimination half-life of unchanged ciprofloxacin is 3 – 5 hours. The elimination kinetics are linear.

Renal clearance is between 180 – 300 mL/kg/h and the total body clearance is between 480 – 600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1 % of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets core

colloidal silicon dioxide,

magnesium stearate,

maize starch,

microcrystalline cellulose,

sodium starch glycollate.

Film-coating

hydroxyl propyl methyl cellulose,

polyethylene glycol,

purified talc,

titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light

6.5 Nature and contents of container

AUSTELL–CIPROFLOXACIN 250 mg:

Blister pack (Clear PVC film & Printed Aluminium foil) of 1 x 10’s, 1 x 14’s, 10 x 10’s.

White HDPE Securipack of 100 tablets.

AUSTELL–CIPROFLOXACIN 500 mg:

Blister pack (Clear PVC film & Printed Aluminium foil) of 1 x 10’s, 10 x 10’s.

White HDPE Securipack of 100 tablets.

AUSTELL–CIPROFLOXACIN 750 mg:

Blister pack (Clear PVC film & Printed Aluminium foil) of 1 x 10’s, 10 x 10’s.

White HDPE Securipack of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd.

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

AUSTELL-CIPROFLOXACIN 250 mg: 38/20.1.1/0011

AUSTELL-CIPROFLOXACIN 500 mg: 38/20.1.1/0012

AUSTELL-CIPROFLOXACIN 750 mg: 37/20.1.1/0354

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 July 2004

10. DATE OF REVISION OF THE TEXT

22 August 2020