**Approved Professional Information for Medicines for Human Use**

**AUSTELL MOXIFLOXACIN IV 400 mg/250 mL solution for infusion**

**SCHEDULING STATUS**

**S4**

## 1 NAME OF THE MEDICINE

AUSTELL MOXIFLOXACIN IV 400 mg/250 mL solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A single sterile unit of AUSTELL MOXIFLOXACIN IV 250 mL infusion solution contains moxifloxacin hydrochloride equivalent to 400 mg moxifloxacin.

1 mL contains 1,6 mg moxifloxacin (as hydrochloride).

Excipient with known effect: contains 356 mg (16 mmoL) sodium per dose.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for infusion.

Clear, yellow solution.

The osmolality of the solution for infusion is approximately 260 mOsm/kg.

The pH of the solution for infusion is approximately 4,4.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**AUSTELL MOXIFLOXACIN IV 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.**

**AUSTELL MOXIFLOXACIN IV 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.**

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AUSTELL MOXIFLOXACIN IV is indicated for the treatment of the following bacterial infections, where these infections are compliant with the indication context:

- Acute bacterial sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis.*
- Acute bacterial exacerbation 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 of mild to moderate severity caused by *Streptococcus pneumonia* (including penicillin-resistant strains and multi-drug resistant strains*), *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumonia*, *Klebsiella pneumoniae*, methicillin sensitive *Staphylococcus aureus* or *Moraxella catarrhalis*.
- 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.*
- Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis) not caused by *Neisseria gonorrhoea.*

- Severe and/or complicated intra – abdominal infections including polymicrobial infections such as abscesses.

Appropriate culture and susceptibility tests should be performed prior to treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to AUSTELL MOXIFLOXACIN IV.

Therapy with AUSTELL MOXIFLOXACIN IV 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.

*Penicillin-resistant *Streptococcus pneumonia* (PRSP) are those strains with a penicillin MIC value of ≥ 2 µg/mL.

Multi-drug resistant *Streptococcus pneumonia* (MDRSP) includes isolates known as PRSP, and are strains resistant to two or more of the following antibiotic classes: penicillin (MIC of ≥ 2 µg/mL), second-generation cephalosporins (e.g. cefuroxime), macrolides, tetracyclines, and trimethoprim/ sulphamethoxazole.

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 MOXIFLOXACIN IV.

Therapy with MOIFLOXACIN IV 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

The recommended dose for AUSTELL MOXIFLOXACIN IV is 400 mg once-daily for all indications.

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.

Recommended duration of treatment of upper and lower respiratory tract infections:

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

Recommended duration of treatment in skin and soft tissue infections:

- Severe and/or complicated skin and skin structure infections — 7 – 21 days

Recommended duration of treatment for other infections:

- Uncomplicated pelvic inflammatory disease — 14 days
- Severe and/or complicated intra – abdominal infections: total treatment duration for sequential therapy (intravenous followed by oral therapy) — 5 – 14 days

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

**Method of administration - Adults**

AUSTELL MOXIFLOXACIN IV solution for infusion should be infused intravenously over 60 minutes. It can be administered directly or together with compatible infusion solutions (see section 6.2 and 6.6).

<u>Special Populations</u>

*Children*

The use of AUSTELL MOXIFLOXACIN IV in children and adolescents in the growth phase is contraindicated (see section 4.3).

*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, AUSTELL MOXIFLOXACIN IV 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). As 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, AUSTELL MOXIFLOXACIN IV should therefore not be used in these patients.

## 4.3 Contraindications

AUSTELL MOXIFLOXACIN IV is contraindicated in patients with:

- Known hypersensitivity to moxifloxacin or other quinolones, or to any component of AUSTELL MOXIFLOXACIN IV.
- Severe hepatic insufficiency (Child-Pugh C) and in patients with transaminases increase > 5 fold ULN.
- 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.
- Congenital or documented acquired QT prolongation.
- Electrolyte disturbances, particularly in uncorrected hypokalaemia.
- Clinically relevant bradycardia.
- Clinically relevant heart failure with reduced left-ventricular ejection fraction.
- Previous history of symptomatic dysrhythmias.
- A history of convulsions, epilepsy or difficult to control epilepsy disorders.
- 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 AUSTELL MOXIFLOXACIN IV, with angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment and the elderly.
- 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 MOXIFLOXACIN IV is prescribed.

Quinolones distribute well into the breast milk of lactating women. Use of AUSTELL MOXIFLOXACIN IV in pregnancy and breastfeeding mothers is contraindicated.

AUSTELL MOXIFLOXACIN IV is contraindicated in children under 18 years and in growing adolescents. Experimental evidence indicates that species variable reversible lesions of the cartilage of weight bearing joints has been seen in immature members of certain animal species.

AUSTELL MOXIFLOXACIN IV should not be used concurrently with other medicines that prolong the QT interval (see section 4.5).

### 4.4 Special warnings and precautions for use

The use of AUSTELL MOXIFLOXACIN IV should be avoided in patients who have experienced serious adverse reactions in the past when
using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with AUSTELL MOXIFLOXACIN IV should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see section 4.3).

Paediatric population, adolescents, pregnancy and lactation
The safety and effectiveness of AUSTELL MOXIFLOXACIN IV in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established (see section 4.3 and 4.6).

<u>Prolongation of the QTc interval and potentially QTc-prolongation-related clinical conditions</u>

AUSTELL MOXIFLOXACIN IV has been shown to prolong the QTc interval on the electrocardiogram in some patients. The magnitude of QT prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion. Therefore, the duration of infusion should not be less than the recommended 60 minutes and the intravenous dose of 400 mg once a day should not

be exceeded (see section 4.3 and 4.5).

Treatment with AUSTELL MOXIFLOXACIN IV should be stopped if signs or symptoms that may be associated with cardiac arrhythmia occur during treatment, with or without ECG findings.

AUSTELL MOXIFLOXACIN IV 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) antidysrhythmic medicines, due to the lack of clinical experience with AUSTELL MOXIFLOXACIN IV in these patient populations.

An additive effect of moxifloxacin, such as in AUSTELL MOXIFLOXACIN IV and other medicines that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded; therefore AUSTELL MOXIFLOXACIN IV should be used with caution when given concurrently with these medicines.

The effect of moxifloxacin, such as in AUSTELL MOXIFLOXACIN IV on patients with congenital prolongation of the QT interval has not been studied; however, it is expected that these individuals may be more susceptible to medicine induced QT prolongation. AUSTELL MOXIFLOXACIN IV should be used with caution in patients with ongoing prodysrhythmic conditions, such as clinically significant bradycardia and acute myocardial ischaemia, as there is limited clinical experience in these patients.

QT prolongation may lead to an increased risk for ventricular dysrhythmias including torsade de pointes.

Female patients and elderly patients may be more sensitive to the effects of QTc-prolonging medications such as AUSTELL MOXIFLOXACIN IV and therefore special caution is required.

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

Therefore, AUSTELL MOXIFLOXACIN IV, 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.

Hypersensitivity/allergic reactions

In patients receiving AUSTELL MOXIFLOXACIN IV, serious and occasionally fatal hypersensitivity reactions such as anaphylaxis, some following the first dose, have been reported. 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). AUSTELL MOXIFLOXACIN IV should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, may be administered as indicated.

Effects on the CNS (Central Nervous System)

Seizures have been reported in patients receiving quinolones, such as in AUSTELL MOXIFLOXACIN IV. AUSTELL MOXIFLOXACIN IV may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, in some cases, suicidal thoughts or acts.

These reactions may occur following the first dose. Should such reactions occur in patients receiving AUSTELL MOXIFLOXACIN IV, AUSTELL MOXIFLOXACIN IV should be discontinued and the

appropriate measures instituted. AUSTELL MOXIFLOXACIN IV 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 the patient to seizures or lower the seizure threshold (see section 4.8).

Other central nervous system (CNS) events that may be caused by quinolones, such as in AUSTELL MOXIFLOXACIN IV include: nervousness, agitation, insomnia, anxiety, nightmares or paranoia.

Antibiotic-associated diarrhoea including colitis

Antibiotic-associated diarrhoea (AAD) and antibiotic-associated colitis (AAC), including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, have been reported in association with the use of AUSTELL MOXIFLOXACIN IV[-] and may range in severity from mild diarrhoea to fatal colitis.

During treatment with antibacterial medicines such as AUSTELL MOXIFLOXACIN IV, the normal flora of the colon is altered and may permit overgrowth of clostridia. A toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis.”

Pseudomembranous colitis has been reported with the use of AUSTELL MOXIFLOXACIN IV and it is important to consider this diagnosis in patients who present with diarrhoea following administration of AUSTELL MOXIFLOXACIN IV. Should this occur, adequate therapeutic measures should be initiated immediately.

Mild cases of pseudomembranous colitis usually respond to discontinuation of AUSTELL MOXIFLOXACIN IV. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial medicine clinically effective against *C.difficile.*

Tendon inflammation, tendon rupture

Tendon inflammation and rupture (especially Achilles tendon), sometimes bilateral, may occur with AUSTELL MOXIFLOXACIN IV, even within 48 hours of starting treatment and have been reported up to several months after discontinuation of therapy. The risk of tendinitis and tendon rupture is increased in elderly patients and in those receiving concurrent treatment with corticosteroids. At the first sign of pain or inflammation, treatment with AUSTELL MOXIFLOXACIN IV should be discontinued and the affected limb(s) rested. Patients should consult their doctor immediately in order for appropriate treatment to be initiated (e.g. immobilisation) for the affected tendon (see sections 4.3 and 4.8).

IV / oral sequential treatment

The following side effects have a higher frequency in the subgroup of IV / oral sequentially treated patients:

Increased gamma-glutaryl-transferase, ventricular tachydysrhythmias, hypotension, vasodilatation, pseudomembranous colitis (in some cases associated with life-threatening complications), seizures of various clinical manifestations (including grand mal convulsions), hallucinations, renal impairment (which in some cases is due to dehydration), can lead to renal failure, especially in elderly with pre-existing renal disorders.

Photosensitivity reactions

Photosensitivity has been reported with some quinolones such as in AUSTELL MOXIFLOXACIN IV. Patients should be advised to avoid exposure to either ultraviolet (UV) irradiation or extensive and/ or strong sunlight during treatment with AUSTELL MOXIFLOXACIN IV.

Severe liver disorders

AUSTELL MOXIFLOXACIN IV 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 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.

Serious bullous skin reactions

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

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 AUSTELL MOXIFLOXACIN IV. Patients under treatment with AUSTELL MOXIFLOXACIN IV 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 renal impairment

AUSTELL MOXIFLOXACIN IV should be used with caution in elderly patients with renal disorders 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).

Patients with myasthenia gravis

AUSTELL MOXIFLOXACIN IV should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

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, AUSTELL MOXIFLOXACIN IV should be used with caution in these patients.

Dysglycaemia

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported with moxifloxacin, such as in AUSTELL MOXIFLOXACIN IV. 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 4.5).

Peri-arterial tissue inflammation

AUSTELL MOXIFLOXACIN IV is for intravenous administration only. Intra-arterial administration should be avoided as peri-arterial tissue inflammation has occurred following administration by this route.

Interference with biological tests

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

Patients with MRSA infections

Moxifloxacin containing medicines, such as AUSTELL MOXIFLOXACIN IV, are 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.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including AUSTELL MOXIFLOXACIN IV. In some cases, depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behaviour such as suicide attempts (see section 4.8). In the event that the patient develops these reactions, AUSTELL MOXIFLOXACIN IV should be discontinued and appropriate measures instituted. Caution is recommended if AUSTELL MOXIFLOXACIN IV is to be used in psychotic patients or in patients with history of psychiatric disease.

Patients with special cSSSI

Clinical efficacy of moxifloxacin such as in AUSTELL MOXIFLOXACIN IV**,** in the treatment of severe burn infections, fasciitis and diabetic foot infections with osteomyelitis has not been established.

Acute kidney injury

Concomitant use of fluoroquinolones and ACE inhibitors may precipitate acute kidney injury in patients,

especially those with moderate to severe renal impairment and elderly patients (see section 5.3). Renal function should be assessed before initiating treatment and monitored during treatment with AUSTELL MOXIFLOXACIN IV and ACE inhibitors/angiotensin receptor blockers.

Other reactions

Severe and sometimes fatal events, some due to hypersensitivity, and some of uncertain aetiology, have been reported in patients receiving therapy with AUSTELL MOXIFLOXACIN IV. These events 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.

Paediatric population

Due to adverse effects on the cartilage in juvenile animals, the use of AUSTELL MOXIFLOXACIN IV is contraindicated in children and adolescents < 18 years (see section 5.3).

Excipients of AUSTELL MOXIFLOXACIN IV

AUSTELL MOXIFLOXACIN IV contains sodium which should be taken into account in patients on a controlled sodium diet.

## 4.5 Interaction with other medicines and other forms of interaction

Warfarin

Increased anticoagulant effects have been reported in patients concurrently using oral anticoagulants and AUSTELL MOXIFLOXACIN IV. 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 dosage of the oral anticoagulant adjusted accordingly.

Medicines prolonging the QT interval

Concurrent use of AUSTELL MOXIFLOXACIN IV and medicines which prolong the QT interval, is contraindicated: Class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) antiarrythmics, antipsychotics (e.g. phenothiazines, pimozide, haloperidol, sultopride), tricyclic antidepressants, certain antimicrobial medicines (saquinavir, erythromycin IV, pentamidine, antimalarials like halofantrine) and medicines such as cisapride and erythromycin.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

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

Charcoal

Concomitant administration of charcoal with a dose of 400 mg intravenous AUSTELL MOXIFLOXACIN IV will reduce systemic availability of the medicine by more than 20 %.

Medicines metabolised by cytochrome P450 enzymes

*In vitro* studies indicate that AUSTELL MOXIFLOXACIN IV does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2. This suggests that AUSTELL MOXIFLOXACIN IV is unlikely to alter the pharmacokinetics of medicines metabolised by these enzymes (e.g. midazolam, ciclosporin, warfarin, theophylline).

Other medicines

The pharmacokinetics of the following medicines are not significantly affected by AUSTELL

MOXIFLOXACIN IV (and vice versa): digoxin, itraconazole, theophylline. The pharmacokinetics of atenolol are also not significantly altered by AUSTELL MOXIFLOXACIN IV.

Antidiabetics

Concomitant administration of oral moxifloxacin with glibenclamide resulted in a decrease of approximately 21 % in the peak plasma concentrations of glibenclamide. The observed pharmacokinetic changes for glibenclamide did not result in changes of the pharmacodynamic parameters (blood glucose, insulin). Therefore, no clinically relevant interaction was observed between moxifloxacin and glibenclamide.

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients with moderate to severe renal impairment and the elderly (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Pregnancy:

The safe use of AUSTELL MOXIFLOXACIN IV in pregnancy has not been established. Use of AUSTELL MOXIFLOXACIN IV is contraindicated in pregnancy (see section 4.3).

Lactation:

There is no data available in lactating or breastfeeding women for moxifloxacin, quinolones distribute well into the breast milk of lactating women. Use of moxifloxacin in breastfeeding mothers is therefore contraindicated (see section 4.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects of moxifloxacin on the ability to drive and use machines have been performed.

AUSTELL MOXIFLOXACIN IV can cause dizziness (see section 4.8). Patients should be cautioned to only drive or operate machinery once they are aware of how AUSTELL MOXIFLOXACIN IV affects them.

## 4.8 Undesirable effects

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

| **System Organ Class (MedDRA)** | **Frequent** | **Less frequent** | **Frequency not known** |
|---|---|---|---|
| **Infections and Infestations** | Superinfections due to resistant bacteria or fungi e.g. oral and vaginal candidiasis | | |
| **Blood and lymphatic system disorders** | | Anaemia, leucopenia, neutropenia, thrombocytopenia, thrombocythemia, blood eosinophilia, prothrombin time | |

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|---|---|---|---|
| | | prolonged / increased INR, increased prothrombin level / decreased INR , agranulocytosis, pancytopenia | |
| **Immune system disorders** | | Allergic reaction, anaphylaxis incl. life-threatening shock, allergic oedema / angioedema (incl. potentially life threatening laryngeal oedema) | |
| **Endocrine disorders** | | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) | |
| **Metabolism and nutrition disorders** | | Hyperlipidaemia, hyperglycaemia, hyperuricaemia, hypoglycaemia, hypoglycaemic coma | |
| **Psychiatric** | | Anxiety reactions, | |

| | | | |
|---|---|---|---|
| **disorders*** | | psychomotor hyperactivity / agitation, emotional lability, depression (in some cases potentially culminating in self-endangering behaviour, such as suicidal ideation/ thoughts, or suicide attempts), hallucination, delirium, depersonalisation, psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideation/ thoughts, or suicide attempts), | |
| **Nervous system disorders*** | Headache, dizziness | Paraesthesia, dysaesthesia, taste disorders | |

| | | | |
|---|---|---|---|
| | | (including ageusia), confusion and disorientation, sleep disorders (predominantly insomnia), tremor, vertigo, somnolence, hypoaesthesia smell disorders (including anosmia), abnormal dreams, disturbed coordination (including gait disturbances, especially due to dizziness or vertigo), leading to fall with injuries, especially in the elderly; Guillain-Barré Syndrome, seizures (incl. grand mal convulsions), | |

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|---|---|---|---|
| | | 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), photophobia, transient loss of vision (especially in the course of CNS reactions), 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 tachyarrhythmias, syncope (i.e. acute and short lasting loss of consciousness), aortic aneurysm and dissection, unspecified arrhythmias, torsade de pointes[#], cardiac arrest[#] [#](especially in patients with severe prodysrhythmic conditions such as clinically significant bradycardia, acute myocardial ischemia*)* | |
| **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 cases associated with life threatening complications) | |
| **Hepatobiliary disorders** | Increase in transaminases, increased | Hepatic impairment (including increase LDH), | |

| | | | |
|---|---|---|---|
| | gamma-glutamyl-transferase, | increased bilirubin, increase in blood alkaline phosphatase, jaundice, hepatitis (predominantly cholestatic), fulminant hepatitis potentially leading to life-threatening liver failure (incl. fatal cases) | |
| **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) |
| **Musculoskelet** | | Arthralgia, | Rhabdomyolysis |

| | | | |
|---|---|---|---|
| **al and connective tissue disorders*** | | myalgia, tendinitis, muscle cramps, muscle twitching, muscle weakness, tendon rupture, arthritis, muscle rigidity, exacerbation of symptoms of myasthenia gravis | |
| **Renal and urinary disorders** | | Dehydration, renal impairment (incl. increase in BUN and creatinine), renal failure | |
| **General disorders and administrative site conditions*** | Injection and infusion site reactions | Feeling unwell (predominantly asthenia or fatigue), painful conditions (incl. pain in back, chest, pelvic and extremities), sweating, infusion site | |

| | | | |
|---|---|---|---|
| | | reactions (thrombo-)<br>phlebitis),<br>oedema | |

*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).

**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 “6.4 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 moxifloxacin and may include nausea, vomiting and diarrhoea (see section 4.8). No specific countermeasures after accidental overdosage are recommended. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. General symptomatic therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg intravenous moxifloxacin will reduce systemic availability of the medicine by more than 20 %.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones, ATC code: J01MA14.

### Microbiology

Moxifloxacin shows *in vitro* activity against a wide range of Gram-positive and Gram-negative bacteria. *In vitro* sensitivity may not always have been confirmed in clinical infection (see section 4.2). Moxifloxacin exerts its antibacterial action by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV which are enzymes required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety of moxifloxacin contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety.

As the mechanism of action for quinolones, including moxifloxacin, differs from that of the macrolides, beta-lactams, aminoglycosides, or tetracycline antibiotics; microorganisms resistant to these classes of antibiotics 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.

| |
|---|
| **Inherently resistant organisms** |
| Aerobic gram-negative micro-organisms: *Pseudomonas aeruginosa* |
| **Species for which acquired resistance may be a problem** |
| Aerobic Gram-positive micro-organisms: *Enterococcus faecalis**, *Enterococcus faecium** |
| Aerobic Gram-negative micro-organisms: *Enterobacter cloacae**, *Escherichia coli**[#], *Klebsiella oxytoca*, *Klebsiella pneumoniae**[#], *Proteus mirabilis** |
| Anaerobic micro-organisms: *Bacteroides fragilis** |

*Activity has been satisfactorily demonstrated.

[#]ESBL-producing strains are commonly also resistant to fluoroquinolones.

## 5.2 Pharmacokinetic properties

Following a single 400 mg intravenous 1 hour infusion of moxifloxacin, peak plasma concentrations of approximately 4,1 mg/L were observed at the end of the infusion. Mean peak plasma concentrations of 4,4 mg/L were observed at steady-state.

Pharmacokinetics are linear up to 600 mg single intravenous dose and up to 600 mg once daily dosing over 10 days.

Distribution

Moxifloxacin is distributed to extravascular spaces. Exposure to moxifloxacin in terms of AUC is high. Volume of distribution at steady state (Vss) amounts to approximately 2 L/kg. In saliva, peak concentrations similar to those of plasma may be reached. Moxifloxacin shows low protein binding (approximately 45 %) and hence high free peak concentrations of > 10 x MIC are observed. Moxifloxacin is mainly bound to serum albumin.

In tissues like lung (epithelial fluid, alveolar macrophages, biotic tissue), the sinuses (maxillary and ethmoid sinus, nasal polypi) and inflamed lesions (cantharide blister fluid), concentrations exceeding those of the plasma are reached.

The following peak concentrations were observed following intravenous administration of a single dose of moxifloxacin (400 mg):

| **Tissue** | **Concentration (mg/L)** | **Site: Plasma ratio** |
|---|---|---|
| Plasma | 4,1 | - |
| Saliva | 5,0 | 0,82-1,37 |
| Blister fluid | 1,75 (1) | 1,7 (1) |
| Interstitial fluid | 1,0 (2) | 0,8-2,5 (2,3) |

(1) 10 h after administration (2) unbound concentration (3) from 3 h up to 36 h post dose

Metabolism

Moxifloxacin undergoes Phase II biotransformation to two inactive metabolites: a sulfo-compound (M1) and a glucuronide (M2).

Excretion

Excretion is via both renal and biliary/faecal pathways as unchanged moxifloxacin as well as the two inactive metabolites (M1 and M2). The sulpho-compound (M1) is excreted mainly in the faeces and the glucuronide compound (M2) exclusively in the urine.

The mean terminal half-life of moxifloxacin elimination from plasma and saliva is approximately 12 hours. The mean apparent total body clearance following a 400 mg dose ranges from 179 to 246 mL/min. Renal clearance amounts to about 24 to 53 mL/min which is suggestive of partial tubular reabsorption of moxifloxacin from the kidneys.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride

Sodium hydroxide solution (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

Water for injection

### 6.2 Incompatibilities

The following co-infusions are incompatible with AUSTELL MOXIFLOXACIN IV:

Sodium Chloride 10 % and 20 % (Precipitation can occur at higher ratios)

Sodium Bicarbonate 4,2 % and 8,4 % (causes pH shift, and $CO_2$ bubbles can form).

AUSTELL MOXIFLOXACIN IV must not be mixed with other products except those mentioned in section 6.6.

### 6.3 Shelf life

Unopened bottle: 3 years.

### 6.4 Special precautions for storage

Store in the original packaging until required for use.

Store at or below 25 °C. Do not refrigerate or freeze.

Protect from light. Keep the bottles in the outer cartons until required for use.

### 6.5 Nature and contents of container

Opaque polypropylene bottles oversealed with either a transparent moulded plastic cap, a grey coloured rubber gasket and a pull ring or a twin port cap, which includes the rubber gasket on the inside and two pull rings on the outside. Bottles are packed in a cardboard box in packs of 1, 5, 10, 12 or 24 bottles. Not all pack sizes are necessarily marketed.

### 6.6 Special precautions for disposal and other handling

The following co-infusions were found to form stable mixtures over a period of 24 hours at room temperature with AUSTELL MOXIFLOXACIN IV, and can therefore be considered compatible:

Water for Injections

Sodium Chloride 0,9 %

Sodium Chloride 1 molar

Glucose 5 %

Glucose 10 %

Glucose 40 %

Ringer solution

Lactated ringer solution

If AUSTELL MOXIFLOXACIN IV is to be given with another medicine, each medicine should be administered separately. Use only clear solutions.

Do not administer if the solution is cloudy.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

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## 8 REGISTRATION NUMBER(S)

50/20.1.1/0434

## 9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

23 November 2017

## 10 DATE OF REVISION OF THE TEXT

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