AUSTRALIAN PRODUCT INFORMATION – MOXIFLOXACIN APO (moxifloxacin hydrochloride)

1. NAME OF THE MEDICINE

Moxifloxacin hydrochloride monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Moxifloxacin APO (moxifloxacin hydrochloride) is a synthetic broad spectrum antibacterial agent.

Each tablet contains 436.3 mg moxifloxacin hydrochloride, equivalent to 400 mg moxifloxacin.

Moxifloxacin APO tablets are available as a 400 mg film-coated tablet for oral administration.

Excipient with known effect: The film-coated tablet contains 223.7 mg lactose per tablet.

For the full list of excipients, see Section 6.1 LIST OF EXIPIENTS.

3. PHARMACEUTICAL FORM

Moxifloxacin APO tablets are dull red coloured, caplet shaped, film coated tablets, debossed with "M" on one side and "400" on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Moxifloxacin APO (moxifloxacin hydrochloride) tablets are indicated for the treatment of adults with infections caused by susceptible organisms in the conditions:

- Acute bacterial sinusitis
- Community acquired pneumonia
- Acute exacerbations of chronic bronchitis

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. Therapy with Moxifloxacin APO may be initiated, in some conditions, before results of these tests are known. Once results become available, therapy should be continued with the most appropriate antibiotic therapy.

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Moxifloxacin injection is unavailable in this brand however is available in other brands. Where correct dosing requires moxifloxacin injection formulation, refer to the specific product information for this formulation for their complete dosage and administration instructions.

The usual dose of Moxifloxacin is 400 mg orally or intravenously every 24 hours. The recommended dose should not be exceeded. The duration of therapy depends on the type of infection as described below.

Infection	Daily Dose	Usual Duration
Acute bacterial sinusitis	400 mg	10 days (oral therapy)
Acute bacterial exacerbations of chronic bronchitis	400 mg	5 days (sequential IV/oral therapy*, oral therapy)
Community acquired pneumonia	400 mg	10 days (oral therapy)
	400 mg	7 – 14 days (sequential IV/oral therapy)

* when caused by organisms bacteriologically proven to be resistant to other classes of antibiotics or when there is intolerance to other antibiotics

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

Oral doses should be administered at least two hours before or four hours after antacids containing magnesium or aluminium, products containing iron, or multivitamins containing zinc. The film-coated tablet should be swallowed whole with sufficient liquid and may be taken independent of meals.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with moxifloxacin IV may be switched to moxifloxacin tablets when clinically indicated at the discretion of the physician.

Dose Adjustments

Elderly

No adjustment of dose is necessary.

Paediatric

The use of Moxifloxacin in children is not recommended (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Interethnic differences

No adjustment of dosage is required in different ethnic groups.

Hepatic impairment

No dosage adjustment is required in patients with impaired liver function. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Moxifloxacin in this patient group is not recommended (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for use in Child Pugh C patients).

Renal impairment

No dosage adjustment is required in renally impaired patients (including patients whose creatinine clearance ≤ 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.

4.3 CONTRAINDICATIONS

Known hypersensitivity to any component of moxifloxacin or to any other quinolones or any of the excipients.

Because of an effect of moxifloxacin on the QTc interval of the electrocardiogram and a lack of clinical experience with the drug in the following patient populations, the drug is contraindicated in patients with known prolongation of the QTc interval, patients with uncorrected hypokalaemia and patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - General, Paediatric Use sub-sections and Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Paediatric sub-section.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Moxifloxacin injection is unavailable in this brand, however this dosage form is available in other brands. Special Warnings and Precautions For Use, Pharmacokinetic and Pharmacodynamic information obtained using moxifloxacin injection formulation is also included in the following sections for prescriber information.

Identified Precautions

Fluoroquinolones, including moxifloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see below in this section ‘

Effects on the CNS’) and musculoskeletal system (see below in this section ‘Effects on Tendons’).

General

The safety and effectiveness of Moxifloxacin in paediatric patients, adolescents (less than 18 years of age), pregnant women and lactating women have not been established. See Section 4.6 FERTILITY, PREGNANCY AND LACTATION.

Cardiac effects

At high concentrations, moxifloxacin is an inhibitor of the delayed rectifier potassium current of the heart. Moxifloxacin has been shown to prolong the QTc interval in some patients. The magnitude of this effect may increase with increasing concentrations of the drug, therefore the recommended dose or infusion rate (400 mg within 60 minutes) should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) and cardiac arrest.

In 787 patients receiving oral treatment with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of moxifloxacin 400 mg on the QTc interval was small (6 ± 26 ms). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval.

Following a course of daily intravenous dosing (400 mg; 1 hour infusion each day) the mean change in QTc from the Day 1 pre-dose value was 9 ms (± 24) on Day 1 (n = 69) and 3 ms (± 29) on Day 3 (n = 290). In sequential IV/oral trials in community acquired pneumonia, QT interval prolongation was reported in 1.3% (6/550) in the moxifloxacin group and 0.7% (4/579) in the comparator group. No cases of ventricular arrhythmia associated with QT interval prolongation was observed in these studies.

No cardiovascular morbidity or mortality was attributed to moxifloxacin among over 5000 patients treated with oral Moxifloxacin including 223 patients who were hypokalaemic at the start of treatment.

Due to limited clinical experience, patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving drugs that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmics, should not receive Moxifloxacin. An additive effect of moxifloxacin and drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants cannot be excluded, therefore Moxifloxacin should be used with caution when given concurrently with these drugs. The effect of moxifloxacin on patients with congenital prolongation of the QTc interval has not been studied, however, it is expected that these individuals may be more susceptible to drug induced QTc prolongation.

Moxifloxacin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients), such as clinically significant bradycardia and acute myocardial ischaemia.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics including moxifloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with moxifloxacin use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Effects on Tendons

Tendon inflammation and rupture that required surgical repair or resulted in prolonged disability have been reported with quinolone therapy including moxifloxacin, particularly in elderly patients and in those treated concurrently with corticosteroids; cases occurring up to several months after completion of therapy have been reported. Moxifloxacin should be discontinued at the first sign of pain, inflammation, or rupture of a tendon and the affected limb(s) rested.

Effects on the CNS

Seizures may occur with quinolone therapy. Moxifloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose them to seizures or lower the seizure threshold. Moxifloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated.

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including Moxifloxacin. Moxifloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including moxifloxacin. In very rare cases depression or psychotic reactions have progressed to suicidal thoughts and self-injurious behavior such as suicide attempts (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In the event that the patient develops these reactions, Moxifloxacin should be discontinued and appropriate measures instituted. Caution is recommended if Moxifloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Paediatric Use

The oral administration of moxifloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Therefore, Moxifloxacin should not be used in paediatric patients.

Use in the Elderly

No data available.

Patients with severe hepatic impairment

As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Moxifloxacin in this patient group is not recommended. Cases of fulminant hepatitis potentially leading to life threatening liver failure (including fatal cases) have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of 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.

Photosensitivity Potential

Phototoxicity has been reported with other quinolones. However, in specially designed preclinical and clinical studies photosensitivity has not been observed with moxifloxacin. In addition, since first marketed there has been no clinical evidence that moxifloxacin causes photosensitivity reactions. Nevertheless, patients should be advised to avoid extensive exposure to either UV irradiation or sunlight.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions have been reported following the first dose. In very rare instances these can progress to life-threatening shock. Moxifloxacin should be discontinued and appropriate therapy commenced in these cases.

Skin Reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacin (see Section 4.8 ADVERSE EFFECTS Post-Marketing Adverse Event Reports). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Osteomyelitis

In patients with complicated skin and skin structure infection who have associated osteomyelitis there are no data demonstrating the efficacy and safety of treatment with Moxifloxacin.

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with Moxifloxacin. In Moxifloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Other

Moxifloxacin is not recommended for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) infections. In case of a suspected or confirmed infection due to MRSA, treatment with an appropriate antibacterial agent should be started (see Section 5.1 PHARMACODYNAMIC PROPERTIES)

Moxifloxacin *in vitro* activity may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Moxifloxacin.

Anaphylactic reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases, the treatment with Moxifloxacin has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Effects on Laboratory Tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The potential for pharmacokinetic drug interactions between moxifloxacin and theophylline, warfarin, digoxin, probenecid, ranitidine, glyburide, iron, and antacids has been evaluated. No clinically significant drug-drug interactions were found with theophylline, warfarin, digoxin, probenecid, ranitidine or glibenclamide, but, as with all other quinolones, iron and antacids significantly reduced the bioavailability of orally administered moxifloxacin. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

There is limited information available on the potential for a pharmacodynamic interaction in humans between moxifloxacin and other drugs that prolong the QTc interval of the electro-cardiogram. In clinical trials, over 200 moxifloxacin-treated patients receiving drugs that prolong the QTc interval, 44 had electrocardiograms before and during moxifloxacin treatment. These patients demonstrated less of a change in QTc on moxifloxacin (1 ± 35 ms) than patients not receiving drugs that prolong the QTc interval (7 ± 25 ms). However, sotalol, a Class III antiarrhythmic, has been shown to further increase the QTc interval when combined with intravenous (IV) moxifloxacin in dogs. Therefore, Moxifloxacin should not be used with Class IA or Class III antiarrhythmics. (See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Drugs which can affect moxifloxacin

See Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for drugs known to prolong the QT interval.

Antacids, minerals and multi-vitamins

Concomitant ingestion of moxifloxacin together with antacids, minerals and multi-vitamins may result in impaired absorption of the drug due to the formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to lower than desired plasma concentrations. Hence, oral doses of Moxifloxacin should be administered at least 2 hours before or four hours after ingestion of antacids, and other preparations containing magnesium, aluminium, sucralfate and other minerals such as iron or zinc.

Anti-retroviral drugs

Oral doses of Moxifloxacin should be administered at least 2 hours before or after ingestion of antacid buffered anti-retroviral drugs (e.g. didanosine).

Drugs shown not to affect moxifloxacin

For the following substances absence of a clinically relevant interaction with moxifloxacin was proven: atenolol, ranitidine, calcium supplements, theophylline, oral contraceptives, glibenclamide, itraconazole, digoxin, morphine, probenecid. No dose adjustment is necessary for these drugs.

Ranitidine

The concomitant administration with ranitidine did not change the absorption characteristics of moxifloxacin significantly. Absorption parameters (C_{max}, t_{max}, AUC) were very similar indicating an absence of influence of gastric pH on moxifloxacin uptake from the gastrointestinal tract.

Calcium supplements

When given with high dose calcium supplements only a slightly reduced rate of absorption was observed while extent of absorption remained unaffected. The effect of high dose calcium supplements on the absorption of moxifloxacin is considered as clinically not relevant.

Warfarin

No interaction during concomitant treatment with warfarin on prothrombin time and other coagulation parameters has been observed.

Changes in INR (International Normalized Ratio): Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with antibiotics, including moxifloxacin. The infectious disease (and its accompanying inflammatory process), age and general status of the patient are risk factors. Although an interaction between moxifloxacin and warfarin was not demonstrated in clinical trials, INR monitoring should be performed, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Oral contraceptives

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

Itraconazole

Exposure (AUC) to itraconazole was only marginally altered under concomitant moxifloxacin treatment. Pharmacokinetics of moxifloxacin were not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with Moxifloxacin and vice versa.

Digoxin

The pharmacokinetics of digoxin are not significantly influenced by moxifloxacin (and vice versa). After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30% at steady state without affecting AUC or trough levels.

Morphine

Parenteral administration of morphine with moxifloxacin did not reduce the oral bioavailability of moxifloxacin and only slightly decreased C_{max} (17%).

Atenolol

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

Theophylline

No influence of moxifloxacin on theophylline pharmacokinetics (and vice versa) at steady state was detected, indicating that moxifloxacin does not interfere with the 1A2 subtypes of the cytochrome P450 enzymes; theophylline concentrations were not elevated at steady state

during combined treatment with moxifloxacin (C_{max} 10.5 vs 10.1 mg/L without vs with theophylline).

Probenecid

No significant effect on apparent total body clearance and renal clearance of moxifloxacin was found in a clinical study investigating the impact of probenecid on renal excretion. Therefore, dosing adjustments need not be made when both drugs are administered concurrently.

Antidiabetic agents

No clinically relevant interaction was seen between glibenclamide and moxifloxacin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Oral treatment of male rats with a dose of 500 mg/kg/day moxifloxacin (about 2.5 times clinical exposure, based on AUC) or an intravenous dose of 45 mg/kg/day (about 0.5 times clinical exposure, based on the estimated AUC) had no effect on fertility. At the oral dose of 500 mg/kg/day there were slight effects on sperm morphology (head-tail separations) in male rats. Female rat fertility was unaffected by the same oral moxifloxacin dose, which resulted in a low relative systemic drug exposure (0.4 times clinical exposure), and slightly reduced oestrus cycling. Female rat fertility was also unaffected by an IV dose of 45 mg/kg/day (about 0.3 times clinical exposure, based on the estimated AUC).

Use in Pregnancy (Category B3)

Reproductive studies performed in rats, rabbits and monkeys indicate that placental transfer of moxifloxacin occurs. Moxifloxacin was not teratogenic in Cynomolgous monkeys administered oral doses of 100 mg/kg/day moxifloxacin (approximately 2 times clinical exposure at the maximum recommended dose based on AUC). Doses of 30 mg/kg/day and above (about 0.6 times clinical exposure in terms of the AUC) resulted in embryonic deaths and abortions. An increased incidence of smaller foetuses was observed at doses of 100 mg/kg/day. Teratogenicity was not seen in a study in rats, but the highest oral dose used (500 mg/kg/day) resulted in a lower (0.25 times) plasma drug exposure than would have been expected during therapy. The same oral dose given to rats from early gestation through to weaning was maternotoxic and was associated with reduced pup weights and increased perinatal mortality. Intravenous administration of 80 mg/kg/day to pregnant rats resulted in maternal toxicity and a marginal effect on fetal and placental weights and the appearance of the placenta. There was no evidence of teratogenicity at intravenous doses as high as 80 mg/kg/day (at least 0.2x clinical exposure, based on AUC). Intravenous administration of 20 mg/kg/day moxifloxacin (approximately equal to clinical exposure in terms of the AUC) to rabbits resulted in decreased fetal body weights, delayed fetal skeletal ossification, an increased incidence of fetuses and litters with malformations and an increased incidence of fetuses with prominent liver lobulation. Maternal toxicity in rabbits at 20 mg/kg/day intravenously included mortality, abortions, reduction of food consumption, decreased water intake, body weight loss and hypoactivity.

There are no adequate or well-controlled studies in pregnant women and because of the above findings in animal teratology studies, moxifloxacin therapy during pregnancy is not recommended.

Use in Lactation

Preclinical evidence indicates that small amounts of moxifloxacin may be secreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking Moxifloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Moxifloxacin may cause dizziness and light-headedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery, or engage in activities requiring mental alertness or co-ordination.

Fluoroquinolones including moxifloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions and vision disorders (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse drug reactions (ADRs) based on all clinical studies with moxifloxacin 400 mg (oral and sequential therapy) sorted by CIOMS III categories of frequency (overall n = 12,984, including n = 2,535 for sequential therapy studies; status: December 2005) are listed below:

ADRs listed under “common” were observed with a frequency below 3% with the exception of nausea and diarrhoea.

Within each frequency grouping, the ADRs are presented in order of decreasing seriousness. Frequencies are defined as:

Common	≥	1/100	to <	1/10
Uncommon	≥	1/1000	to <	1/100
Rare	≥	1/10000	to <	1/1000
Very rare	<	1/10000		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Infections and Infestations	Mycotic superinfections			
Blood and the Lymphatic System Disorders		Anaemia Leucopaenia(s) Neutropaenia Thrombocytopaenia Thrombocythaemia Prothrombin time prolonged/INR increased	Thromboplastin level abnormal	Prothrombin level increased/INR decreased Prothrombin level/INR abnormal
Immune System Disorders		Allergic reaction Pruritis Rash Urticaria Blood eosinophilia	Anaphylactic/anaphylactoid reaction Allergic oedema/angioedema (incl. laryngeal oedema, potentially life threatening)	Anaphylactic/anaphylactoid shock (potentially life threatening)

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
Metabolism and Nutrition Disorders		Hyperlipidaemia	Hyperglycaemia Hyperuricaemia	
Psychiatric Disorders		Anxiety reactions Psychomotor hyperactivity/agitation	Emotional lability Depression Hallucinations	Depersonalisation Psychotic reactions
Nervous system disorders	Headache Dizziness	Par- / Dysaesthesia Taste disorder (incl. ageusia in very rare cases) Confusion and disorientation Sleep disorder Tremor Vertigo Somnolence	Hypoaesthesia Smell disorders (incl. anosmia) Abnormal dreams Disturbed coordination (incl. gait disturbances, esp. due to dizziness or vertigo; Seizures of various clinical manifestations (incl. grand mal convulsions) Disturbed attention Speech disorders Amnesia Peripheral neuropathy and polyneuropathy	Hyperaesthesia
Eye Disorders		Visual disturbances (especially in the course of CNS reactions)		Transient loss of vision (especially in the course of CNS reactions)
Ear and Labyrinth Disorders			Tinnitus Hearing impairment including deafness (usually reversible)	
Cardiovascular System Disorders	QT prolongation in patients with hypokalaemia	QT prolongation Palpitations Tachycardia Vasodilatation	Ventricular tachyarrhythmias Syncope Hypertension Hypotension	Unspecified arrhythmias
Respiratory, thoracic and mediastinal Disorders		Dyspnoea (including asthmatic conditions)		
Gastrointestinal Disorders	Nausea Vomiting Gastrointestinal and abdominal pains Diarrhoea	Decreased appetites and food intake Constipation Dyspepsia Flatulence Gastroenteritis (excl. erosive gastroenteritis) Increased amylase	Dysphagia Stomatitis Antibiotic associated colitis (in very rare cases associated with life threatening complications)	
Hepatobiliary Disorders	Increase in transaminases	Hepatic impairment (incl. LDH increase) Increased bilirubin Increased gamma-glutamyl-transferase Increase in blood alkaline phosphatase	Jaundice Hepatitis (predominantly cholestatic)	
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia Myalgia	Tendonitis Increased muscle tone and cramping Muscular weakness	Arthritis
Renal and Urinary Disorders			Renal impairment Renal failure (due to dehydration	

System Organ Class (MedDRA)	Common	Uncommon	Rare	Very Rare
			esp. in elderly with pre-existing renal disorders)	
General Disorders		Feeling unwell Unspecific pain Sweating	Oedema	

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

Common: Increased gamma-glutamyl-transferase

Uncommon: Hallucination, Seizures of various clinical manifestations (incl. grand mal convulsions), Hypotension, Oedema, Antibiotic-associated colitis (in very rare cases associated with life threatening complications), Ventricular tachyarrhythmias, Renal impairment and Renal failure (due to dehydration esp. in elderly with pre-existing renal disorders).

Post-Marketing Adverse Event Reports

Cardiovascular System Disorders:

very rare (<0.01%): cardiac arrest and torsade de pointes, and usually in patients with concurrent severe underlying proarrhythmic conditions such as clinically significant bradycardia, acute myocardial ischaemia.

Hepatobiliary Disorder:

very rare (<0.01%): fulminant hepatitis potentially leading to life-threatening liver failure (including fatal cases).

Musculoskeletal, Connective Tissue and Bone Disorder:

very rare (<0.01%): tendon rupture, gait disturbance (caused by muscular, tendon or joint symptoms), exacerbation of symptoms of myasthenia gravis.

Psychiatric Disorders:

very rare (<0.01%): depression and/or psychotic reactions potentially culminating in self-injurious behaviour such as suicidal ideational thoughts or suicide attempts.

Nervous System Disorders:

very rare (<0.01%): disturbed coordination leading to fall with injuries (esp. in elderly).

Skin and Subcutaneous Tissue Disorders:

very rare (<0.01%): bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis (potentially life threatening).

Renal and Urinary Disorders:

uncommon (≥0.1% to <1%): dehydration (caused by diarrhoea or reduced fluid intake).

Metabolism and Nutrition Disorders:

Hypoglycaemia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Only limited data on overdose are available. Single oral doses of up to 2.8 g and multiple doses of 600 mg over 10 days were administered to healthy subjects without any significant undesirable effects. In the event of overdosage it is recommended that appropriate supportive care should be instituted as dictated by the patient's clinical status. The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase in systemic moxifloxacin exposure. Due to the potential for moxifloxacin to cause QT prolongation, patients should be carefully monitored following an overdose.

Concomitant dosing of charcoal and 400 mg oral moxifloxacin reduced the systemic availability of the drug by more than 80% by preventing absorption in vivo. The application of activated charcoal in the early absorption phase prevents further increase of systemic exposure in cases of overdose.

Contact Poisons Information Centre 131126 for advice on management.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Moxifloxacin is an 8-methoxyfluoroquinolone antibiotic with a broad spectrum of activity and bactericidal action. The bactericidal action results from the inhibition of topoisomerase II or DNA gyrase and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

Moxifloxacin exhibits concentration dependent bactericidal killing. Minimum bactericidal concentrations are generally similar to minimum inhibitory concentrations. The mechanism of action for quinolones, including moxifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to moxifloxacin. There is no known cross-resistance between moxifloxacin and other classes of antibiotics. Although cross-resistance has been observed between moxifloxacin and other fluoroquinolones against gram-negative bacteria, gram-positive bacteria resistant to other fluoroquinolones may be susceptible to moxifloxacin.

Moxifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in Section 4.1 THERAPEUTIC INDICATIONS.

Gram-positive bacteria	*Gram-negative bacteria*	*Others*
Streptococcus pneumoniae (penicillin-susceptible strains) *Staphylococcus aureus* (methicillin-susceptible strains) *Streptococcus pyogenes (group A)*	*Haemophilus influenzae* *Haemophilus parainfluenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Escherichia coli* *Enterobacter cloacae*	*Chlamydia pneumoniae* *Mycoplasma pneumoniae*

Moxifloxacin exhibits *in vitro* activity ($MIC_{90} \leq 2$ µg/mL) against the following microorganisms, but their clinical significance is unknown.

Gram-positive bacteria	*Gram-negative bacteria*	*Anaerobes*
Streptococcus pneumoniae (including penicillin and macrolide resistant strains) *Streptococcus milleri* *Streptococcus mitior* *Streptococcus agalactiae*	*Klebsiella oxytoca* *Proteus mirabilis* *Citrobacter freundii*	*Fusobacterium spp.* *Prevotella spp.* *Peptostreptococcus* spp
		Others
		Legionella pneumophila *Coxiella burnetti*

Moxifloxacin does not reliably show activity against *Pseudomonas aeruginosa.*

Resistance

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not interfere with the antibacterial activity of moxifloxacin. Other resistance mechanisms such as permeation barriers and efflux mechanisms may, however, also affect the sensitivity of corresponding bacteria to moxifloxacin. Plasmid-mediated resistance has not been observed to date.

Cross resistance among quinolones has been observed. As moxifloxacin inhibits both topoisomerases II and IV, some gram-positive bacteria and anaerobes that are resistant to other quinolones are susceptible to moxifloxacin.

The frequency of acquired resistance may vary geographically and with time for certain species. Local area information on resistance of organisms is desirable, particularly when treating severe infections.

Effect on the Intestinal Flora in Humans

In two volunteer studies, the following changes in intestinal flora were seen following dosing with moxifloxacin. *E. coli*, *Bacillus* spp., *Bacteroides vulgatus*, *Enterococci* and *Klebsiella* spp. were reduced, as were the anaerobes *Bifidobacterium*, *Eubacterium* and *Peptostreptococcus*. These changes returned to normal within two weeks. *Clostridium difficile* toxin was not found.

Susceptibility Tests

Dilution or diffusion techniques - either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS).

Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of **"Intermediate" indicates that the result should be considered equivocal, and, if the** microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from **causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen** is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Clinical Trials

In this section, overall clinical response is defined as the combined response rate at the end of treatment and follow-up visits (with failures at the end of treatment carried forward) in the per-protocol population. Bacteriological eradication is defined as eradication plus presumed eradication in microbiologically valid patients.

Acute bacterial exacerbation of chronic bronchitis

Moxifloxacin tablets (400 mg once daily for 5 days) were evaluated for acute bacterial exacerbation of chronic bronchitis in two large randomised, double-blind, controlled clinical studies. Clarithromycin (500 mg twice daily) was used as the active control in both studies and the treatment duration was 7 days in one study (0124), and 10 days in the other (0127). The overall clinical response and bacteriological eradication rates for the most frequently isolated pathogens are as follows:

	Moxifloxacin	**Clarithromycin**
Overall clinical response		
Study 0124	82% (271/331)	80% (270/338)
Study 0127	89% (222/250)	89% (224/251)
Bacteriological eradication*		
Haemophilus influenzae	90% (73/81)	76% (54/84)
Streptococcus pneumoniae	83% (48/54)	95% (56/59)
Moraxella catarrhalis	86% (43/50)	98% (47/48)

* Study 0124 and 0127 combined

Community acquired pneumoniae

Three large randomised, double-blind controlled clinical studies were conducted to evaluate the efficacy of Moxifloxacin tablets (400 mg once daily for 10 days) in patients with clinically and radiologically documented community acquired pneumonia. Clarithromycin (500 mg twice daily for 10 days) was used as the active control in two studies (0119 and 0130) and high dose amoxycillin (1000 mg three times daily for 10 days) in the remaining one (0140). The results of these studies are as follows:

	Moxifloxacin	**Clarithromycin**
Overall clinical response		
Study 0119	93% (141/152)	92% (141/153)

Study 0130	95% (184/194)	95% (178/188)
Bacteriological eradication*		
Streptococcus pneumoniae	95% (36/38)	94% (29/31)
Haemophilus influenzae	97% (35/36)	81% (21/26)
Moraxella catarrhalis	83% (10/12)	100% (4/4)
Chlamydia pneumoniae	92% (47/51)	98% (48/49)
Mycoplasma pneumoniae	96% (23/24)	100% (20/20)
	Moxifloxacin	**Amoxycillin**
Overall clinical response		
Study 0140	89% (143/160)	89% (159/178)
Bacteriological eradication		
Streptococcus pneumoniae	90% (43/48)	85% (39/46)
Haemophilus influenzae	100% (9/9)	83% (15/18)

* Study 0119 and 0130 combined

Sequential IV/Oral Therapy

Two large, randomised, controlled trials were conducted to compare the efficacy of sequential IV/PO Moxifloxacin 400 mg QD for 7-14 days in the treatment of patients with clinically and radiologically documented mild-moderate or severe community acquired pneumonia. A double-blind study enrolled 516 patients from the U.S. and Canada compared Moxifloxacin to an IV/PO fluoroquinolone control. Another study enrolled 628 patients from Europe, Israel and South Africa, and compared Moxifloxacin to sequential IV/PO amoxicillin/clavulanate (1.2 g IV q8h/625 mg PO q8h) with or without high-dose IV/PO clarithromycin (500 mg BID). The primary efficacy analysis was conducted in clinically evaluable patients at the test of cure visit (Day 7-30 post-therapy for NA Study and Day 5-7 post-therapy for Ex-NA Study). The clinical success rate for Moxifloxacin therapy was equivalent to the fluoroquinolone comparators (86% vs. 89%). The clinical success for Moxifloxacin therapy (93%) was higher than that for amoxicillin/clavulanate ± clarithromycin (85%) [95% C.I. for the treatment difference was 2.9% to 13.2%].

The microbiological eradication rates (eradication plus presumed eradication) in Moxifloxacin treated patients from these two trials were *Streptococcus pneumoniae* 93% (63/68), *Streptococcus pneumoniae* bacteremia 95% (19/20), *Haemophilus influenzae* 92% (23/25), *Mycoplasma pneumoniae* 96% (22/23), and *Chlamydia pneumoniae* 93% (13/14). Across all Moxifloxacin tablet and intravenous community acquired pneumonia studies, the clinical success for *Legionella pneumophila* was 100% (6/6).

Acute bacterial sinusitis

In a large randomised, double-blind controlled study, Moxifloxacin tablets (400 mg once daily for 10 days) were compared with cefuroxime axetil (250 mg twice daily for 10 days) in the treatment of acute bacterial sinusitis. The results obtained from this study are as follows:

	Moxifloxacin	**Cefuroxime axetil**
Overall clinical response	86% (186/217)	89% (198/222)
Bacteriological eradication		
Streptococcus pneumoniae	95% (36/38)	100% (32/32)
Haemophilus influenzae	100% (17/17)	94% (15/16)
Staphylococcus aureus	100% (14/14)	88% (7/8)
Moraxella catarrhalis	100% (10/10)	100% (5/5)

Skin and Skin Structure Infections

In a prospective, randomized, double-blind, active-control, multi-centre Phase III B clinical study (study number 100273), a total of 617 patients were randomized to one of the two treatment groups (sequential IV/p.o moxifloxacin 400 mg qd versus piperacillin/tazobactam 3.0/0.375 g IV followed by p.o amoxicillin/clavulanic acid suspension 800/114 mg bid). Subjects were enrolled with infections which included infected ischaemic or decubitus ulcers, diabetic foot infections, major abscesses, carbuncles, other SSTI requiring surgery, post-operative surgical infections and infected bite wounds. The clinical success rate (clinical cure or resolution) at the Test of Cure (TOC) visit was 79.4% (143/180) and 81.8% (153/187) for the moxifloxacin and comparator groups, respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-12.04, +3.29 95% CI).

In a second study prospective, non-blind, comparative, parallel group, multicentre, multinational Phase III clinical study (study number 10279) in patients with cSSSi with 804 patients, the patients were randomly and equally assigned to one of the two treatment groups: sequential IV/PO moxifloxacin 400 mg QD or amoxicillin/clavulanate 1000/200 mg IV followed by 500/125 mg PO TID, and maintained on a non-blind basis.

The clinical success rate at the TOC visit was 80.6% (254/315) and 84.5% (268/317) for the moxifloxacin and comparator groups respectively. Moxifloxacin was proven to be no less effective than the comparator regimen (-9.41, +2.18 95% CI).

The clinical cure rates for the patients at TOC visit analysed by diagnosis type for each study are as follows:

	Moxifloxacin	**Piperacillin/ tazobactam 3.0/0.375g IV followed by oral amoxicillin/ clavulanic acid 800/114mg BID**	**Moxifloxacin**	**Amoxicillin/ clauvulanate 1000/200mg IV followed by oral 500/125mg TID**
	(n=180)	**(n=187)**	**(n=315)**	**(n=317)**
	Study 100273		Study 10279	
Overall Clinical Response	143/180 (79%)	153/187 (82%)	254/315 (81%)	268/317 (85%)
Skin abscess	42/53 (79%)	52/56 (93%)	92/98 (94%)	82/93 (88%)
Cellulitis/erysipelas[a]	36/43 (84%)	38/45 (84%)	99/110 (90%)	105/112 (94%)
Diabetic foot infection	25/37 (68%)	25/41 (61%)	25/49 (51%)	42/63 (67%)
Fasciitis	NA	NA	11/22 (50%)	7/13 (54%)
Surgical wound infection	11/12 (92%)	8/8 (100%)	8/9 (89%)	12/13 (92%)
Infected ischemic ulcers	10/13 (77%)	6/10 (60%)	2/6 (33%)	4/4 (100%)
Infection of traumatic lesion[b]	11/12 (92%)	10/13 (77%)	17/21 (81%)	16/19 (84%)
Other infection types[c]	8/10 (80%)	12/14 (86%)	NA	NA

a includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis and complicated erysipelas

b includes infection of traumatic lesion, bite wound infection and infection with trauma.

c includes infected hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infections, infection of deep soft tissue and lymphangitis.

The bacteriological eradication rates at TOC by baseline pathogen for selected organisms in the patients with causative organisms follows:

	Study 100273		**Study 10279**	
	Moxifloxacin n/N (%)	**Comparator n/N (%)**	**Moxifloxacin n/N (%)**	**Comparator n/N (%)**
Staphylococcus aureus	50/64 (78%)	47/59 (80%)	48/59 (81%)	71/78 (91%)
Streptococcus pyogenes	13/18 (72%)	8/12 (67%)	9/15 (60%)	8/9 (89%)
Escherichia coli	7/8 (88%)	11/12 (92%)	24/30 (80%)	16/20 (80%)
Klebsiella pneumoniae	5/6 (83%)	4/7 (57%)	5/5(100%)	2/2 (100%)
Enterobacter cloacae	4/5 (80%)	1/2 (50%)	5/6 (83%)	2/4 (50%)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, moxifloxacin is absorbed rapidly and almost completely with an absolute bioavailability of approximately 90%.

Concomitant administration of moxifloxacin together with food slightly prolongs the time to reach peak concentrations by approximately 2 hours and slightly reduced peak concentrations by approximately 16%. Extent of absorption remained unchanged. As AUC/MIC is most predictive for antimicrobial efficacy of quinolones, this effect is clinically not relevant. Therefore, Moxifloxacin can be administered independent from meals.

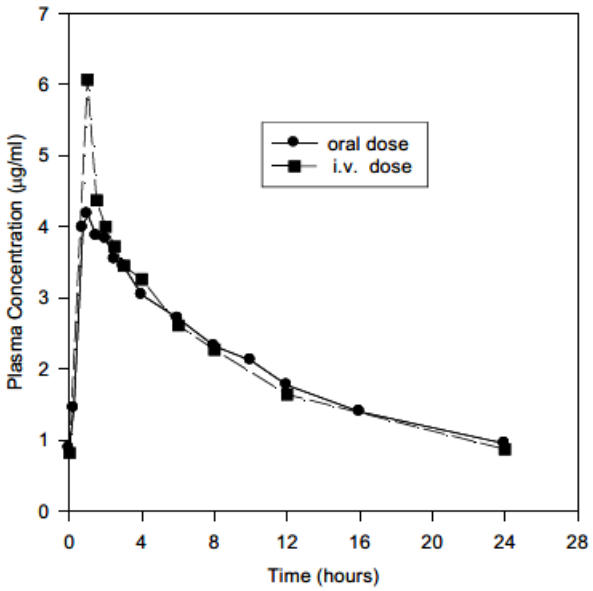
The mean (± SD) C_{max} and AUC values following single and multiple doses of 400 mg moxifloxacin given orally or by 1 hour i.v. infusion are summarised below.

	C_{max} (mg/L)	**AUC (mg.h/L)**	**Half-life (hr)**
Single Dose Oral			
Healthy (n = 372)	3.1 ± 1.0	36.1 ± 9.1	11.5 - 15.6*
Single Dose I.V.			
Healthy young (n = 56)	3.9 ± 0.9	39.3 ± 8.6	8.2 - 15.4*
Patients (n = 118)		-	
Male (n = 64)	4.4 ± 3.7		
Female (n = 54)	4.5 ± 2.0		
< 65 years (n = 58)	4.6 ± 4.2		
> 65 years (n = 60)	4.3 ± 1.3		
Multiple Dose Oral			
Healthy young male/female (n = 15)	4.5 ± 0.5	48.0 ± 2.7	12.7 ±1.9
Healthy elderly male (n = 8)	3.8 ± 0.3	51.8 ± 6.7	
Healthy elderly female (n = 8)	4.6 ± 0.6	54.6 ± 6.7	
Healthy young male (n = 8)	3.6 ± 0.5	48.2 ± 9.0	
Healthy young female (n = 9)	4.2 ± 0.5	49.3 ± 9.5	
Multiple Dose I.V.			
Healthy young male (n = 8)	4.2 ± 0.8	38.0 ± 4.7	14.8 ± 2.2
Healthy elderly (n =12; 8 male, 4 female)	6.1 ± 1.3	48.2 ± 0.9	10.1 ± 1.6
Patients (n = 107)		-	

	C_{max} (mg/L)	AUC (mg.h/L)	Half-life (hr)
Male (n = 58)	4.2 ± 2.6		
Female (n = 49)	4.6 ± 1.5		
< 65 years (n = 52)	4.1 ± 1.4		
> 65 years (n = 55)	4.7 ± 2.7		

* range of means from different studies

Mean Steady-State Plasma Concentrations of Moxifloxacin Obtained with Once Daily Dosing of 400 mg Either Orally (n=10) or by I.V. Infusion (n=12)



Plasma concentrations increase proportionately with dose up to the highest dose tested (1200 mg single oral dose). The mean (± SD) elimination half-life from plasma is 12 ± 1.3 hours; steady-state is achieved after at least three days with a 400 mg once daily regimen.

Distribution

The mean volume of distribution at steady state (Vss) is approximately 2 L/kg. In *in vitro* and *ex vivo* experiments protein binding over a range of 0.02 to 2 mg/L resulted in a protein binding of approximately 40 - 42% independent of the drug concentration. Moxifloxacin is mainly bound to serum albumin.

Moxifloxacin is widely distributed throughout the body. Moxifloxacin has been detected in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses following oral or intravenous administration of 400 mg. Concentrations measured at 3 hours post-dose are summarised in the following table. The rates of elimination of moxifloxacin from tissues generally parallel the elimination from plasma.

Moxifloxacin Concentrations (mean ± SD) in Plasma and Tissues Measured 3 Hours After Oral Dosing with 400 mg

Tissue or Fluid	Plasma Concentration (μg / mL)	Tissue or Fluid Concentration (μg / mL or μg/ g)	Tissue: Plasma Ratio
Respiratory			
Alveolar macrophages	3.3 ± 0.7	61.8 ± 27.3	21.2 ± 10.0
Bronchial mucosa	3.3 ± 0.7	5.5 ± 1.3	1.7 ± 0.3
Epithelial lining fluid	3.3 ± 0.7	24.4 ± 14.7	8.7 ± 6.1
Sinus			
Maxillary sinus mucosa	3.7 ± 1.1	7.6 ± 1.7	2.0 ± 0.3
Anterior ethmoid mucosa	3.7 ± 1.1	8.8 ± 4.3	2.2 ± 0.6
Nasal polyps	3.7 ± 1.1	9.8 ± 4.5	2.6 ± 0.6
Skin, Musculoskeletal			
Blister fluid	3.0 ± 0.5	2.6 ± 0.9	0.9 ± 0.2

The peak concentrations and site vs. plasma concentration ratios for various target tissues yielded comparable results for both modes of drug administration after a single dose of 400 mg moxifloxacin.

Metabolism

Moxifloxacin is metabolised via glucuronide and sulphate conjugation. The cytochrome P450 system is not involved in moxifloxacin metabolism and is not affected by moxifloxacin. M1 and M2 are the only metabolites relevant in humans and both are microbiologically inactive. The sulphate conjugate (M1) accounts for approximately 38% of the dose and is eliminated primarily in the faeces. Approximately 14% of an oral or intravenous dose is converted to glucuronide conjugate (M2) which is excreted exclusively in the urine. Peak plasma concentrations of M2 are approximately 40% those of the parent drug, while plasma concentrations of M1 are generally less than 10% those of moxifloxacin.

Excretion

Approximately 45% of an oral or intravenous dose is excreted as unchanged drug (~20% in urine and ~25% in faeces). A total of 96% ± 4% of an oral dose is excreted as either unchanged drug or known metabolites. The mean apparent total body clearance and renal clearance are approximately 12 L/hr and 2.5 L/hr, respectively suggesting partial tubular reabsorption of the drug from the kidneys.

Special Populations

Geriatric

In a study of 16 healthy elderly male and female volunteers given a single oral 200 mg dose of moxifloxacin, the AUC, C_{max} and elimination half life were not statistically different between young and elderly subjects. In large phase III studies, the pharmacokinetics in elderly patients following intravenous infusion of 400 mg were similar to those observed in young patients. Therefore dosage adjustments based on age are not necessary.

Paediatric

The pharmacokinetics of moxifloxacin have not been studied in paediatric patients.

Sex

Following oral administration of 400 mg moxifloxacin daily for 10 days to 23 healthy males (19-75 years) and 24 healthy females (19-70 years), the mean AUC and C_{max} were 8% and 16% higher, respectively, in females compared to males. Dosage adjustments based on sex are not necessary.

Interethnic differences

Possible interethnic differences were examined in Caucasian, Japanese, Black and other ethnic groups. No clinically relevant interethnic differences in pharmacokinetics could be detected.

Renal impairment

The pharmacokinetics of moxifloxacin are not significantly changed by renal impairment (including creatinine clearance < 30 mL/min/1.73m^2) and in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis. No dose adjustment is therefore required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1.73m^2). In a single oral dose study in patients with varying degrees of renal impairment not requiring dialysis, the mean AUC was increased by 13% in patients with moderate (Clcr ≥ 30 and ≤ 60 mL/min) and severe (Clcr < 30 mL/min) renal impairment. Mean AUC of the sulphate metabolite increased by 1.7 fold and the glucuronide increased by 2.8 fold.

Hepatic impairment

Moxifloxacin plasma concentrations of patients with mild to severe hepatic impairment (Child Pugh A to C) did not reveal clinically relevant differences compared to healthy volunteers or patients with normal hepatic function, respectively (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - *Patients with severe hepatic impairment*). In a single oral dose study in patients with stable chronic liver cirrhosis, concentrations of moxifloxacin were reduced by approximately 23% while concentrations of the sulphate metabolite were increased almost four-fold. No dosage adjustment for mild to moderate hepatic impairment is recommended. As limited clinical data are available in severe hepatic impairment (Child Pugh C), the use of Moxifloxacin in this patient group is not recommended.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 32 healthy volunteers (8 per group), no photosensitivity was produced by moxifloxacin. The minimum erythematous dose (MED) was measured before and after treatment with moxifloxacin (200 mg or 400 mg once daily), lomefloxacin (400 mg once daily), or placebo, and in this study, both doses of moxifloxacin were equivalent to placebo, while lomefloxacin significantly lowered the MED.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Moxifloxacin was not mutagenic in 4 of 5 strains in the Salmonella reversion assay, however, as with other quinolones, a positive response was observed in strain TA 102. This may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay and gave an equivocal result in the V79/HGPRT mammalian cell gene mutation assay. Moxifloxacin was clastogenic in the v79 chromosome

aberration assay *in vitro* but inactive *in vivo* in dominant lethal and micronucleus tests in mice. Moxifloxacin was inactive in an assay for unscheduled DNA synthesis *in vitro*.

Carcinogenicity

Conventional long term carcinogenicity studies in rodents have not been carried out. Moxifloxacin at an oral dose of 459 mg/kg/day, was inactive in a limited 38 week tumor-initiation–promotion bioassay in rats. This dose resulted in a systemic drug exposure that was 1.9 times (males) and 0.3 (females), compared with the clinical exposure at the maximum recommended clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXIPIENTS

Besides the active ingredient, Moxifloxacin APO tablets also contain the following excipients:
Lactose (223.7mg/tablet)
Povidone
Croscarmellose Sodium
Colloidal Anhydrous Silica
Magnesium Stearate
Titanium dioxide
Hypromellose
Macrogol 400
Iron oxide red

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Moxifloxacin APO tablets should be stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Moxifloxacin APO tablets are packaged in blister strips (PVC/PVdC/aluminium) in packs of 5 tablets and are available in one strength.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

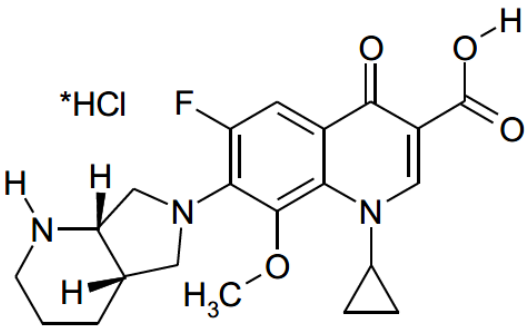
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Moxifloxacin, a fluoroquinolone, differs from other quinolones in that it has a methoxy function at the 8-position and an *S,S* configurated diazabicyclononyl ring moiety at the 7-position.

Chemical Name: 1-cyclopropyl-7-{(*S*,*S*)-2,8-diaza-bicyclo[4.3.0]non-8-yl}-6-fluoro-8methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid hydrochloride.



Molecular Formula: $C_{21}H_{23}FN_3O_4$ * HCl

Molecular Weight: 437.9

CAS Number

186826-86-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Plunkett Consulting Pty Ltd.
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171 Union Rd
Surrey Hills 3027
Victoria
Australia

9. DATE OF FIRST APPROVAL

9 August 2019

10. DATE OF REVISION

Section Changed	Summary of new information