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SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

LONXAVE 100 mg DT (dispersible tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LONXAVE 100 mg DT: Each Dispersible tablet contains: Moxifloxacin Hydrochloride equivalent to Moxifloxacin….100 mg

Contains sugar (91 mg of Mannitol, 3,5 mg of Sucralose and 12,5 mg of Aspartame).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible tablet

LONXAVE 100 mg DT: Light yellow to mottled yellow colour, capsule shape, biconvex, uncoated dispersible tablets debossed with “I 75” on one side and breakline on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LONXAVE DT 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.

LONXAVE DT is not indicated/approved for the initiation of treatment (first-line treatment) of infections

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

Respiratory tract infections:

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

- Acute exacerbations of chronic obstructive pulmonary disease (COPD) including chronic bronchitis (AECB) caused by Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, methicillin-sensitive Staphylococcus aureus or Moraxella catarrhalis.
- Community acquired pneumonia (CAP) of mild to moderate severity caused by Streptococcus pneumoniae (including CAP caused by penicillin-resistant strains and multi-drug resistant strains), Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Klebsiella pneumoniae, methicillin-sensitive Staphylococcus aureus or Moraxella catarrhalis.
- Acute sinusitis caused by Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis.
- Uncomplicated pelvic inflammatory disease (i.e. infections of female upper genital tract, including salpingitis and endometritis) (not caused by Neisseria gonorrhoea) where these infections are compliant with the indication statement, with special reference to the second part of the statement.
- Severe and/or complicated skin and skin structure infections (including diabetic foot infections) caused by methicillin-sensitive Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Streptococcus agalactiae, Klebsiella pneumoniae, Proteus mirabilis, or Enterobacter cloacae. Severe and/or complicated intra-abdominal infections including polymicrobial infections such as abscesses.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate

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and identify organisms causing infection and to determine their susceptibility to **LONXAVE 100 mg DT.** Therapy with **LONXAVE 100 mg DT** may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and method of administration

Posology

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

Duration of treatment:

The duration of treatment should be determined by the severity of the indication or clinical response.

The following general recommendations for the treatment of upper and lower respiratory tract infections are made:

- Acute exacerbation of chronic bronchitis 5 days
- Community acquired pneumonia 7 - 14 days
- Acute sinusitis 10 days

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

- Uncomplicated skin and skin structure infections 7 days
- Complicated skin and skin structure infections 7 – 21 days

The recommended durations for other infections are:

- Uncomplicated pelvic inflammatory disease 14 days
- 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.

Special populations

Elderly:

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No adjustment of dosage is required in the elderly.

Hepatic impairment:

No dosage adjustment is required in patients with mild to moderate impaired liver function (Child-Pugh A and B). No pharmacokinetic data are available for patients with severely impaired liver function (Child-Pugh C). Due to the lack of data **LONXAVE 100 mg DT** is contraindicated in patients with severe hepatic impairment.

Renal impairment:

No dose adjustment is required in patients with any degree of renal impairment (including creatinine clearance < 30 mL/min/1,73m^2) and in patients on chronic dialysis including haemodialysis and continuous ambulatory peritoneal dialysis.

Missed dose and vomiting after a dose:

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to moxifloxacin and reduce its effectiveness.

Method of administration

For oral use.

LONXAVE 100 mg DT may be taken with food or between meals.

The 4 x **LONXAVE 100 mg DT** tablets should be dispersed in 50 mL drinking water (approximately 10 mL per tablet) and thoroughly mixed. The entire mixture (water and tablets) should be swallowed. The mixture should be used within 10 minutes. The cup or glass that contained the mixture should then be rinsed with a small amount of water and the contents swallowed to ensure that the patient takes the entire dose.

4.3 Contraindications

Known hypersensitivity to moxifloxacin, other quinolones or to any component of the **LONXAVE 100 mg DT** listed in **section 6.1**.

Due to the lack of clinical data the use of **LONXAVE 100 mg DT** is not recommended in patients with

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severe hepatic insufficiency (Child-Pugh C). No dosage adjustment is required in patients with mild to moderate hepatic insufficiency (Child-Pugh A and B).

Quinolones are known to distribute well into breast milk of lactating women. The use of **LONXAVE 100 mg DT** in pregnancy and breastfeeding mothers is contra-indicated (see **section 4.6**).

- A history of tendon, muscle, joint, nerve, central nervous system or psychiatric disorders especially those related to previous quinolone/fluoroquinolone use where alternative appropriate antibiotic choices are available.
- A history of convulsions, epilepsy or difficult to control epilepsy disorders.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection where alternative choices are available.
- Myasthenia gravis.
- Congenital or 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.
- **LONXAVE 100 mg DT** should not be used concurrently with other medicines that prolong the QT interval (see **section 4.5**).
- Concomitant use of fluoroquinolones including **LONXAVE 100 mg DT** with ACE inhibitors/Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.
- Use of fluoroquinolones is contraindicated in patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed or is not well tolerated.

4.4 Special warnings and precautions for use

The safety and efficacy of **LONXAVE 100 mg DT** in paediatric patients, adolescents (less than 18 years of age), pregnant and lactating women have not been established (see **section 4.6**).

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Hypersensitivity/allergic reactions

Hypersensitivity and allergic reactions may occur after the first administration.

Anaphylactic reactions can progress to a life-threatening shock, in some instances after the first administration. Hypersensitivity and allergic reactions, including life-threatening anaphylactic/anaphylactoid shock may occur with the first exposure of **LONXAVE 100 mg DT**. In these cases the treatment with **LONXAVE 100 mg DT** must be discontinued and appropriate medical treatment be instituted.

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

MOXIFLOXACIN AS CONTAINED LONXAVE 100 MG DT HAS BEEN SHOWN TO PROLONG THE QT INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. LONXAVE 100 mg DT 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 LACK OF CLINICAL EXPERIENCE WITH LONXAVE 100 MG DT IN THESE PATIENT POPULATIONS (SEE SECTION 4.3).

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 **LONXAVE 100 mg DT** associated effects on the QT interval (see **section 4.3**).

As the magnitude of QT prolongation may increase with increasing concentrations of **LONXAVE 100 mg DT**, the recommended dose and the infusion rate (400 mg within 60 minutes) should not be exceeded.

However, in patients suffering from pneumonia no correlation between plasma concentrations of moxifloxacillin as in **LONXAVE 100 mg DT** and QTc prolongation was observed. QT prolongation may lead to an increased risk of ventricular dysrhythmias including *torsades de pointes*. In patients with paired valid ECGs in Phase III clinical trials, the mean ± SD effect of _moxifloxacillin as in **LONXAVE 100 mg DT** on the QTc interval was 6 ± 26 msec (see **section 4.3**).

Therefore, treatment with **LONXAVE 100 mg DT** should be avoided due to the lack of clinical

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experience with **LONXAVE 100 mg DT** in these patient populations (see **section 4.3**):

- in patients with known prolongation of the QT interval
- in patients with uncorrected hypokalaemia
- in patients receiving class IA (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-dysrhythmic medicines

LONXAVE 100 mg DT should be used with caution as an additive effect of **LONXAVE 100 mg DT** on the QT interval cannot be excluded for the following conditions (see **section 4.3**):

- in patients treated concomitantly with medicines that prolong the QT interval such as cisapride, erythromycin, antipsychotics and tricyclic antidepressants.
- in patients with ongoing dysrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischaemia.
- in patients with liver cirrhosis as pre-existing QT prolongation in these patients cannot be excluded.
- in women and elderly patients who, may be more susceptible to QTc-prolonging medicines.

Patients with myasthenia gravis

LONXAVE 100 mg DT should not be used in patients with myasthenia gravis.

Effects on weight bearing joints

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 medicines also produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species.

Patients predisposed to seizures

Seizures may occur with **LONXAVE 100 mg DT** therapy. It should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure

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threshold (see **section 4.3**).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving quinolones including **LONXAVE 100 mg DT**. Patients under treatment with **LONXAVE 100 mg DT** should be advised to inform their medical practitioner prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of an irreversible condition (see **section 4.8**). The recovery process of neuropathy may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Antibiotic-associated diarrhoea including colitis

Pseudomembranous colitis has been reported with moxifloxacin as in **LONXAVE 100 mg DT** therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of **LONXAVE 100 mg DT**. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Medicines inhibiting peristalsis are contraindicated in patients who develop serious diarrhoea.

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Tendinitis and tendon rupture

Tendinitis may occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Tendinitis and/or tendon rupture may still occur for several months after completion of therapy.

Close monitoring of these patients is therefore necessary if they are prescribed **LONXAVE 100 mg DT**. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with **LONXAVE 100 mg DT** must be stopped immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Prevention of photosensitivity reactions

Phototoxicity has been reported in patients receiving certain quinolones; However, studies have shown that moxifloxacin has a lower risk to induce photosensitivity. Patients should be instructed to avoid excessive sunlight or artificial ultraviolet light (e.g. tanning beds) and contact a medical practitioner if sunburn-like reactions or skin eruptions occur.

Patients with pelvic inflammatory disease

For patients with complicated pelvic inflammatory disease (e.g. associated with a tubo-ovarian or pelvic abscess), for whom an intravenous treatment is considered necessary, treatment with **LONXAVE 100 mg DT** is not recommended. Pelvic inflammatory disease may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Therefore in such cases empirical moxifloxacin should be co-administered with another appropriate antibiotic (e.g. a cephalosporin) unless moxifloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

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Severe liver disorders

Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported with moxifloxacin as in **LONXAVE 100 mg DT** (see **section 4.8**.). Patients should be advised to contact their medical practitioner prior to continuing treatment 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 (see **section 4.3**).

Serious bullous skin reactions

Cases of bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with moxifloxacillin as in **LONXAVE 100 mg DT** (see **section 4.8**). Patients should be advised to contact their medical practitioner immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of quinolones, including **LONXAVE 100 mg DT**. 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, **LONXAVE 100 mg DT** should be discontinued and appropriate measures instituted. Caution is recommended if **LONXAVE 100 mg DT** is to be used in psychotic patients or in patients with history of psychiatric disease (see **section 4.3**).

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, **LONXAVE 100 mg DT** should be

used with caution in these patients.

Interference with biological tests

LONXAVE 100 mg DT therapy may interfere with the Mycobacterium spp. culture test by suppression of mycobacterial growth causing false negative results in samples taken from patients currently receiving **LONXAVE 100 mg DT.**

Patients with MRSA infections

LONXAVE 100 mg DT is not recommended for the treatment of 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**).

Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers in renal impairment and elderly patients

Concomitant use of fluoroquinolones including **LONXAVE 100 mg DT** and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (AKI) in patients, especially those with moderate to severe renal impairment and elderly patients. (**See Section 4.5**). Renal function should be assessed before initiating treatment, and monitored during treatment, with **LONXAVE 100 MG DT** or ACE inhibitors/renin-angiotensin receptor blockers.

Aortic aneurysm and dissection

There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissections, or in the presence of other risk factors or conditions predisposing aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos

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syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known arthrosclerosis) (see **section 4.3**).

In case of sudden abdominal, chest, or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department of a hospital.

Patients with mitral valve and or aortic valve regurgitation

There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones should not be prescribed to patients with mitral valve and or aortic valve regurgitation (**see Section 4.3**)

Patients with renal impairment

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

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see **sections 4.7 and 4.8**).

Dysglycaemia

Disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with moxifloxacillin as in **LONXAVE 100 mg DT** usually in diabetic patients, receiving concomitant treatment with an oral hypoglycaemic medicine (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see **section 4.8**).

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Patients of sodium diet

In patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome) the additional sodium load of the solution for infusion should be taken into account. For sodium chloride content of the solution for infusion see **section 2**.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of LONXAVE 100 mg DT with other medicines that may prolong QT interval:

An additive effect on QT interval prolongation of **LONXAVE 100 mg DT** and other medicines that may prolong the QTc interval cannot be excluded. This might lead to an increased risk of ventricular arrhythmias, including torsade de pointes.

Therefore, co-administration of **LONXAVE 100 mg DT** with any of the following medicines is contraindicated (see **section 4.3**):

- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti- arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressives (e.g. amitriptyline, trimipramine, desimipramine)
- certain antimicrobial medicines (saquinavir, sparfloxacin, erythromycin IV, erythromycin, pentamidine,
- antimalarials particularly halofantrine
- certain antihistaminics (astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

LONXAVE 100 mg DT should be used with caution in patients who are taking medication that can reduce potassium levels (e.g. loop and thiazide-type diuretics, laxatives and enemas (high doses), corticosteroids, amphotericin B) or medication that is associated with clinically significant bradycardia.

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Food and dairy products:

LONXAVE 100 mg DT can be taken with or without food as the absorption of moxifloxacin is not altered by food intake.

Ranitidine:

The concomitant administration with ranitidine which alters the gastric pH, does not change the absorption characteristics of **LONXAVE 100 mg DT** significantly.

Antacids, minerals and multivitamins:

Concomitant ingestion of **LONXAVE 100 mg DT** together with antacids, minerals and multivitamins may result in impaired absorption of **LONXAVE 100 mg DT** due to formation of chelate complexes with the multivalent cations contained in these preparations. This may lead to plasma concentrations considerably lower than desired. Hence, antacids, anti-retroviral medicines and other preparations containing magnesium, aluminium and other minerals such as iron should be administered at least 4 hours before or 2 hours after ingestion of a **LONXAVE 100 mg DT** dose.

Warfarin:

Cases of increased anticoagulant activity have been reported in patients receiving oral anticoagulants concurrently with **LONXAVE 100 mg DT.** International Normalised Ratio (INR) monitoring is recommended, and if necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Digoxin:

The pharmacokinetics of digoxin are significantly influenced by **LONXAVE 100 mg DT.** After repeated dosing in healthy volunteers moxifloxacin increased C_{max} of digoxin by approximately 30 % at steady state without affecting AUC or trough levels. Increased clinical and laboratory monitoring of patients on digitalis therapy is advised.

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Itraconazole:

The pharmacokinetics of **LONXAVE 100 mg DT** are not significantly altered by itraconazole. No dose adjustment is necessary for itraconazole when given with **LONXAVE 100 mg DT** and *vice versa*.

Theophylline:

No influence of **LONXAVE 100 mg DT** on theophylline pharmacokinetics (and *vice versa*) at steady state was detected. Hence, no recommendations with respect to theophylline dosing need to be given.

Antidiabetics:

Concomitant administration of **LONXAVE 100 mg DT** with glibenclamide may result in a decrease of approximately 21 % in the peak plasma concentrations of glibenclamide.

Oral contraceptives:

No interaction has occurred following concomitant oral administration of **LONXAVE 100 mg DT** with oral contraceptives.

Calcium supplements:

No interaction has occurred following concomitant oral administration of **LONXAVE 100 mg DT** with calcium supplements.

Morphine:

Parenteral administration of morphine does not reduce the oral bioavailability of **LONXAVE DT 100 mg.**

Atenolol:

The pharmacokinetics of atenolol are not significantly influenced by **LONXAVE 100 MG DT.**

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Medicines metabolised by Cytochrome P450 enzymes:

In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2, suggesting that **LONXAVE 100 mg DT** is unlikely to alter the pharmacokinetics of medicines metabolised by these enzymes (e.g. midazolam, cyclosporine, warfarin, theophylline).

Nonsteroidal anti-inflammatory drugs (NSAIDs):

The concomitant administration of NSAIDs with **LONXAVE 100 mg DT** may increase the risk of CNS stimulation and convulsions (see **section 4.4.**).

ACE Inhibitors/rennin angiotensin receptor blockers:

Concomitant use of fluoroquinolones including **LONXAVE 100 mg DT** and ACE inhibitors/renin angiotensin receptor blockers may precipitate acute kidney injury (see **section 4.3**).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established. The use of **LONXAVE 100 mg DT** in pregnancy and breastfeeding mothers is contra-indicated (see **Section 4.5**).

Pregnancy

The safety of **LONXAVE 100 mg DT** in human pregnancy has not been evaluated. Animal studies have shown reproductive toxicity. The potential risk for humans is unknown. Due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals and reversible joint injuries described in children receiving some fluoroquinolones, **LONXAVE 100 mg DT** must not be used in pregnant women.

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Breastfeeding

There is no data available in lactating or nursing women. Preclinical data indicate that small amounts of moxifloxacin are secreted in milk. In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of immature animals, breastfeeding is contraindicated during **LONXAVE 100 mg DT** therapy.

Fertility

No data available

4.7 Effects on ability to drive and use machines

LONXAVE 100 mg DT may cause dizziness and light-headedness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

LONXAVE 100 mg DT can have side effects.

Apart from nausea and diarrhoea all adverse reactions were observed at frequencies below 3%.

Table 1: Tabulated summary of adverse reactions

System organ class	**Frequency**	**Undesirable effect**
Infections and infestations	*Frequent*	Mycotic superinfections
Blood and lymphatic system disorders	*Less frequent*	Anaemia, leukopenia, thrombocytopenia, Neutropenia, thrombocythemia, prolonged prothrombin time/increased

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		INR, abnormal thromboplastin level, increased prothrombin level/decreased INR, abnormal prothrombin level/INR, blood eosinophilia. Agranulocytosis and Pancytopenia
Endocrine disorders	*Less frequent:*	Syndrome of inappropriate Antidiuretic hormone secretion (SIADH)
Immune system disorders	*Less frequent:*	Allergic reaction, anaphylactic/anaphylactoid reaction, allergic oedema/angioedema (including laryngeal oedema), anaphylactic/anaphylactoid shock (potentially life-threatening).
Metabolic and nutritional disorders	*Less frequent:*	Hyperlipidaemia, hyperglycaemia, hyperuricaemia. Hypoglycaemia,(particularly in diabetic patients.)
Psychiatric disorders	*Less frequent:*	Anxiety reactions, psychomotor hyperactivity, agitation, emotional lability, depression (potentially culminating in self-endangering behaviour such as suicidal ideation/thoughts of suicide attempts), hallucinations.
	Frequency not known:	Depersonalisation, psychotic reactions (potentially culminating in self-

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		endangering behaviour such as suicidal ideation/thoughts of suicide attempts).
Nervous system disorders	*Frequent*	Headache, dizziness.
	Less frequent:	Paraesthesia, dysaesthesia, taste disorders (including ageusia), confusion and disorientation, sleep disorders, tremor, vertigo, somnolence, hypoaesthesia, smell disorders (including anosmia), abnormal dreams, disturbed coordination (including gait disturbances due to dizziness or vertigo; which may lead to fall with injuries especially in elderly), seizures, disturbed attention, speech disorders, amnesia, peripheral neuropathy, polyneuropathy, Hyperaesthesia.
Eye disorders	*Less frequent*	Visual disturbances, Photophobia, Transient loss of vision, Uveitis and bilateral acute iris transillumination.
Ear and labyrinth disorders	*Less frequent*	Tinnitus, hearing impairment including deafness.
Cardiac disorders	*Frequent*	QT prolongation.
	Less frequent	Palpitations, tachycardia, atrial fibrillation, angina pectoris, ventricular

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		tachyarrhythmias, specified dysrhythmias.
	Frequency not known	*Torsade de Pointes*, cardiac arrest.
Vascular disorders	*Less frequent:*	Vasodilatation, syncope, hypertension, hypotension.
Respiratory, thoracic and mediastinal disorders	*Less frequent:*	Dyspnoea, asthma
Gastrointestinal disorders	*Frequent:*	Nausea, vomiting, gastrointestinal and abdominal pain, diarrhoea.
	Less frequent	Anorexia, constipation, dyspepsia, flatulence, gastroenteritis, increased amylase, dysphagia, stomatitis, pseudomembranous colitis, Clostridium difficile-associated disease (CDAD)
Hepatobiliary disorders	*Frequent:*	Increase in transaminases.
	Less frequent:	Increase in gamma-glutamyl-transferase (gGT), hepatic impairment (including LDH increase), increased bilirubin, increase in alkaline phosphatase, jaundice, hepatitis.
	Frequency not known	Fulminant hepatitis potentially leading to life-threatening liver failure.
Skin and subcutaneous	*Less frequent*	Pruritus, rash, urticaria, sweating.

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tissue disorders	*Frequency unknown*	Bullous skin reactions like Stevens-Johnson Syndrome or toxic epidermal necrolysis (potentially life-threatening), photosensitivity.
Musculoskeletal and connective tissue disorders	*Less frequent*	Arthralgia, myalgia, tendonitis, increased muscle tone and cramping, arthritis, tendon rupture, exacerbation of symptoms of myasthenia gravis, rhabdomyolysis.
Renal and urinary disorders	*Less frequent*	Renal impairment, renal failure, haematuria, dysuria, interstitial nephritis.
General disorders and administrative site conditions	*Less frequent*	Feeling unwell, unspecific pain, oedema, dehydration, asthenia, malaise.

Post-marketing experience

Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor or a contributory factor or played no role in the reported cases where mitral cases and/or aortic regurgitation were diagnosed.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com

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4.9 Overdose

Adverse reactions may be exaggerated or exacerbated. No specific countermeasures after accidental overdosage are recommended. General symptomatic and supportive therapy should be initiated. Concomitant administration of charcoal with a dose of 400 mg oral **LONXAVE 100 mg DT** will reduce systemic availability of the medicine by more than 80 %.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A20.1.1 Broad and medium spectrum antibiotics

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

***Mechanism of action*:**

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

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative micro-organisms.

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair and recombination.

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

Frequently resistant organisms

Aerobic Gram-positive micro-organisms

Enterococcus faecalis

Aerobic Gram-negative micro-organisms

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Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Proteus mirabilis

Anaerobic micro-organisms

Bacteroides fragilis

lnherently resistant organisms

Aerobic Gram-negative micro-organisms

Pseudomonas aeruginosa

Resistant organisms

Staphylococcus aureus (methicillin/ofloxacin resistant strains)

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

5.2 Pharmacokinetic properties

Pharmacokinetics in Adults

Absorption

Moxifloxacin is well absorbed after oral administration. The absolute bioavailability amounts to approximately 90 % after oral administration of a 400 mg dose. Pharmacokinetics are linear in the range of 50 to 1 200 mg single oral dose and up to 600 mg once daily dosing over 10 days. Steady state is reached within 3 days. Following a 400 mg oral dose, peak concentrations of 3,1 mg/ℓ are reached within 0,5 to 4 h post administration. Peak and trough plasma concentrations at steady state (400 mg once daily) were 3,2 and 0,6 mg/ℓ, respectively.

Distribution

Moxifloxacin is distributed to extravascular spaces. Exposure to moxifloxacin in terms of AUC (AUC_{norm} = 6 kg*h/L) is high; the volume of distribution at steady state amounts to Vss of approx. 2 ℓ/kg. In saliva peak concentrations and similar to those of plasma may be reached. Due to low protein

binding (approximately 45 %) high free peak concentrations > 10 x MIC are observed. 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 45 % independent from the concentration of the active. 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.

Biotransformation

Moxifloxacin undergoes Phase II biotransformation and is excreted via renal and biliary faecal pathways as unchanged moxifloxacin as well as in form of a sulfo-compound (M1) and a glucuronide (M2). M1 and M2 are the only metabolites relevant in humans. Both are microbiologically inactive. The recovery from urine (approximately 19 % for unchanged moxifloxacin, approximately 2,5 % for M1 and approximately 14 % for M2) and faeces (approximately 25 % of unchanged moxifloxacin, approximately 36 % for M1 and no recovery for M2) totalled to approximately 96,98 % of the dose independent from the route of administration.

Elimination

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LONXAVE 100 mg DT contains Ethylcellulose, Isopropyl alcohol, Methacrylic acid copolymer,

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Purified water, Triethyl citrate, Mannitol, Microcrystalline cellulose, Sucralose, Sodium Chloride, Crospovidone, Aspartame, Magnesium stearate and Bitter Masker Flavour (OZ-378-740-5) contains Acacia, 414, Sugar, Tapioca maltodextrin, Nature-identical flavouring substance(s), Artificial flavouring substance(s), Ascorbic acid, 300.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months for blister pack.

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light and moisture.

Keep the blisters in the carton until required for use.

KEEP MEDICINE OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Blister pack:

Tablets are packed in cold form 25 µm OPA/45 µm aluminum foil/60 µm PVC as the forming material and 25 µ aluminium plain foil/ 6-8 gsm heat seal lacquer as the lidding material, packed in a pre-printed carton.

Pack size includes 10's, 28's, 30's and 100's Tablets.

Not all pack sizes may be marketed.

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6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Ground Floor, Block 1,

Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock Ext 12,

Alberton, Gauteng

8. REGISTRATION NUMBERS

LONXAVE 100 mg DT : 60/20.1.1/0617

9. DATE OF FIRST AUTHORISATION

LONXAVE 100 mg DT : 26 May 2026

10. DATE OF REVISION OF THE TEXT

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