APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

LOXIP 250 mg (Tablet)

LOXIP 500 mg (Tablet)

COMPOSITION:

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

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

The other ingredients are cellulose, microcrystalline; sodium starch glycolate; povidone; silica, colloidal anhydrous and magnesium stearate and opadry white.

Opadry white contains hypromellose, macrogol and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Ciprofloxacin is a synthetic fluroquinolone antibiotic. It is bactericidal and acts by inhibiting the A subunit of DNA-gyrase which is essential in the reproduction of bacterial DNA.

Micro-organisms resistant to ciprofloxacin:

Enterococcus faecium; Norcardia asteroides; Ureapiasma urealyticum; Peptostreptococcus species; Peptococcus species*;* Bacteroides*; Treponem a pallidum; Staphylococcus aureus (methicillin-resistant), Stenotrophomonas maltophilia, Actinomycas, Listeria monocytogenes and Mycoplasma genitalium.*

Pharmacokinetics

After oral administration, ciprofloxacin plasma levels are dose-related and peak

at 0,5 - 2 hours. The absolute bioavailability is approximately 70 %. Protein binding is 40 %. Forty to fifty percent is excreted in urine as unchanged ciprofloxacin. Approximately 15% of a single dose is eliminated as metabolites.

Elimination is primarily renal and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 ml/minute. The elimination half-life of unchanged ciprofloxacin is 3 - 5 hours. The elimination kinetics are linear.

INDICATIONS:

LOXIP is indicated for the treatment of the following infections, when caused by susceptible organisms:

Lower respiratory tract infections caused by:

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

Urinary tract infections caused by:

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

Skin and soft tissue infections caused by:

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

Gastro-intestinal infections:

Infective diarrhoea caused by *Campylobacter jejuni, Escherichia cofi, Shigella flexneri* and *Shigelia sonnei.*

Bone Infections:

Osteomyelitis due to sensitive Gram-negative organisms.

Gonorrhoea: (except that is due to *N. gonorrhoeae*)

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

CONTRA-INDICATIONS:

LOXIP is contra-indicated in patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or any of the inactive ingredients of **LOXIP**.

Pregnancy and lactation:

LOXIP is contra-indicated in children under the age of 18 years and in growing adolescents.

Experimental evidence indicates lesions of the cartilage of weight-bearing joints in immature members of certain animal species.

WARNINGS AND SPECIAL PRECAUTIONS:

LOXIP should be used in caution with patients with a history of convulsive disorders.

Crystalluria related to the use of **LOXIP** has been observed. Patients receiving **LOXIP** should be well hydrated and excessive alkalinity of the urine should be avoided.

Special Precautions:

Severe infections and/or infections due to Gram-positive or anaerobic bacteria

For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, **LOXIP** should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumonia infections

LOXIP should not be used for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumonia.*

Genital tract infections

Genital tract infections may be caused by fluoroquinolone-resistant *Nesseria gonorrhoeae* isolates. In genital tract infections thought to be due to *N. Gonorrhoeae,* **LOXIP** should not be used.

Cardiac disorders

LOXIP is associated with cases of QT prolongation. In general, elderly patients may be more susceptible to **LOXIP**-associated effects on the QT interval. Precaution should be taken when using **LOXIP** with concomitant medicinal products that can result in prolongation of the QT interval (e.g. class IA or III antidysrhythmics) or in patients with risk factors for torsades de pointes (e.g. known QT prolongation, uncorrected hypokalaemia).

Hypersensitivity

In some instances, hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately. Anaphylactic/anaphylactoid reactions can progress to life threatening shock, even after the first administration. In these cases **LOXIP** has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Gastrointestinal system

In the event of severe and persistent diarrhoea during or after treatment a doctor must be consulted, since this symptom can hide a serious intestinal disease (life threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment. In such cases, **LOXIP** must be discontinued and appropriate therapy initiated. Medicines that inhibit peristalsis are contraindicated.

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Musculoskeletal system

At any sign of tendonitis (e.g. painful swelling) the administration of **LOXIP** should be discontinued, physical exercise should be avoided, and a medical practitioner consulted. Tendon rupture (predominantly Achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids and in patients with kidney or lung transplant. Close monitoring of these patients is necessary if they are prescribed **LOXIP**. The risk is still present weeks after completion of treatment.

Nervous system

In patients with epilepsy and in patients who have suffered from previous CNS- disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), **LOXIP** should only be used where the benefits of treatment exceed the risks, since these patients are vulnerable because of possible central-nervous side effects.
In some instances the CNS reactions already occurred after the first administration of **LOXIP**. In these cases **LOXIP** must be discontinued and the medical practitioner informed immediately. Depression or psychosis can progress to result in self endangering behaviour.

Skin and appendages

LOXIP has been shown to produce photosensitivity reactions. Patients taking **LOXIP** should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e. sunburn-like skin reactions) occurs. Severe cutaneous adverse reactions (SCARS) including toxic epidermal necrolysis (TEN) Stevens Johnson Syndrome (SJS) and drug reaction with no eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal ,have been reported with **LOXIP** (see section SIDE-EFFECTS).At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and closely monitored. If signs and symptoms suggestive of these reactions appear, **LOXIP** should be

discontinued immediately, and an alternative treatment should be considered. If the patient have developed a serious reaction such as SJS, TEN or DRESS with use of LOXIP,treatment with LOXIP must not be restarted in this patient at any time

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicines which are metabolised via the same enzymatic pathway (e.g. theophylline, methylxanthines, caffeine, duloxetine, clozapine) are administered concomitantly with **LOXIP**. Increased plasma concentrations associated with medicine specific side effects may be observed due to inhibition of their metabolic clearance by **LOXIP** (See **"INTERACTIONS"**).

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin. Causes of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Patients receiving **LOXIP** should be well hydrated and excessive alkalinity of the urine should be avoided.

Long-term or repeated administration of **LOXIP** can lead to superinfections with resistant bacteria or fungi.

Ability to Drive and Use Machines

The ability to drive a motor vehicle or operate machinery may be impaired by **LOXIP**, particularly when used in combination with alcohol.

Side-effects that may be potentially life-threatening are pancytopenia and bone marrow depression (see **"SIDE-EFFECTS"**).

Streptococcus pneumonia infections

LOXIP should not be used for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumonia.*

INTERACTIONS:

Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels.

There is a high risk of tendonitis (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Concurrent administration of **LOXIP** with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related toxicity. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

LOXIP should be administered 1 - 2 hours before, or at least 4 hours after taking iron preparations, antacids containing magnesium, aluminium, calcium or sucralfate, as interference with absorption may occur. This restriction does not apply to antacids belonging to the class of H_2-receptor blockers.

Concomitant administration of the nonsteroidal anti-inflammatory medicines (NSAIDSs), with quinolones such as **LOXIP** may increase the risk of central nervous system stimulation and seizures.

Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed.

The simultaneous administration of **LOXIP** and warfarin may lead to warfarin toxicity; therefore the INR should be closely monitored.

Concurrent administration of **LOXIP** and glibenclamide can potentiate the action of glibenclamide, leading to hypoglycaemia.

Probenecid interferes with renal secretion of **LOXIP**. Co-administration of probenecid and **LOXIP** increases the **LOXIP** serum concentrations.

Metoclopramide accelerates the absorption of **LOXIP**, resulting in a shorter time to reach maximum plasma concentrations.

Concurrent administration of **LOXIP** with ropinirole may lead to elevated plasma concentrations of ropinirole. Monitoring for ropinirole-related side effects and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with **LOXIP**.

Concurrent administration of **LOXIP** with lidocaine (lignocaine) may lead to elevated plasma concentrations of lidocaine and increase in side effects related to lidocaine also occurs.

Concurrent administration of **LOXIP** with clozapine may lead to elevated serum concentrations of clozapine and N-desmethylclozapine. Careful monitoring of clozapine associated adverse effects and appropriate adjustment of clozapine dosage during and shortly after co-administration with **LOXIP** is advised.

Concurrent administration of **LOXIP** with sildenafil may lead to elevated serum concentrations of sildenafil. Therefore, sildenafil should be used with caution when co-administered with **LOXIP**.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (See **"CONTRA-INDICATIONS"**).

On the basis of animal studies, it has been reported that ciprofloxacin, as in **LOXIP** may cause damage to articular cartilage in the fetus. It has also been reported to cause teratogenic effects in animals. Therefore, **LOXIP** should not be given to pregnant women.

Lactation: Ciprofloxacin is excreted in breastmilk. **LOXIP** should not be used during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

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

LOXIP should be swallowed whole with plenty of liquid and may be taken with or without meals.

Dosage and Duration of Treatment:

The dosage range is 250 - 750 mg twice daily. The duration of treatment depends upon the severity of the infection, clinical response and bacteriological cultures. For acute uncomplicated cystitis in women, the treatment period is 3 days. Generally, treatment should be continued for at least 3 days after the signs and symptoms of the infection have disappeared. For acute infections the usual treatment period is 5 - 10 days with **LOXIP**. For severe and complicated infections more prolonged therapy may be required. In streptococcal infections the treatment must last at least 10 days.

Infections of the lower respiratory tract:

Mild to moderate: 250 - 500 mg twice daily.

Severe or complicated: 750 mg twice daily.

In cystic fibrosis patients: 750 mg twice daily. The low body mass of these patients should, however, be taken into consideration when determining dosage (7,5 to 15 mg/kg/day).

Infections of the urinary tract:

Acute uncomplicated cystitis: 250 mg twice daily.

Mild to moderate: 250 mg twice daily.

Severe or complicated: 500 mg twice daily.

Infections of the skin:

Mild to moderate: 500 mg twice daily.

Severe or complicated: 750 mg twice daily.

Infectious diarrhoea: 500 mg twice daily.

Bone Infections:

Mild to moderate: 500 mg twice daily.

Severe or complicated: 750 mg twice daily.

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

Gonorrhoea: A single dose of 250 mg.

Elderly patients should be treated with the lowest possible dose.

Impaired Renal or Liver Function:

In patients with reduced renal function, the half-life of ciprofloxacin may be prolonged. The dosage needs to be adjusted as shown below.

For patients with renal impaired and hepatic insufficiency, monitoring of medicine serum levels provides the most reliable basis for dose adjustment.

<u>Dose adjustment of ciprofloxacin for patients with renal or hepatic impairment</u>:

1. Kidney insufficiency:

1.1 Cl_{cr}> 31 mL/min/1,73m^2 Max 800 mg/day intravenously.

1.2 Cl_{cr}< 30 mL/min/1,73m^2 Max 400 mg/day intravenously.

1.3 Impaired renal function

As in 1.2 above; after dialysis and haemodialysis on dialysis days.

2. Renal impairment and CAPD (chronic ambulatory peritoneal dialysis):

2.1. Oral administration of either **LOXIP** as 500 mg tablets or 2 x 250 mg tablets or **LOXIP** suspension equivalent to 500 mg **LOXIP** is indicated.

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

3. **Hepatic impairment**: No dose adjustment.

4. **Hepatic and renal impairment**: As in 1.1 and 1.2 above.

SIDE-EFFECTS:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and the lymphatic system disorders	Frequency unknown	Eosinophilia, leucocytopaenia, granulocytopaenia, anaemia, thrombocytopenia, leucocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values, pancytopenia, bone marrow depression.
Immune system disorders	Frequency unknown	Anaphylactic/anaphylactoid reactions can occur (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), serum sickness-like reaction, in some instances after the first administration. In these cases LOXIP has to be

		discontinued and appropriate medical treatment instituted
Metabolism and nutrition disorders	~~Rare:~~ Less frequent:	hypoglycaemia, particularly in diabetic patients
Psychiatric disorders	Less frequent:	Agitation, anxiety states, confusion, disorientation, hallucinations, psychotic reactions (even progressing to self-endangering behaviour), depression, nightmares.
Nervous system disorders	Less frequent:	Headache, migraine, dizziness, tiredness, nervousness and trembling, hypoaesthesia, paraesthesia, dysaesthesia, hyperaesthesia, linsomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure, seizures, peripheral neuropathy and polyneuropathy.
Eye disorders	Less frequent	Visual disturbances (e.g. diplopia, colour vision).
Ear and labyrinth disorders	Less frequent:	Tinnitus, transient

		impairment of hearing, vertigo, hearing loss.
Cardiac disorders	Less frequent:	Tachycardia, flushes, QT prolongation, ventricular dysrhythmia, Torsades de Pointes
Vascular Disorders	Less frequent:	syncope, hypotension, vasodilatation and vasculitis.
Gastrointestinal disorders	Frequent:	Impaired taste and smell, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain and flatulence. The development of severe and persistent diarrhoea may indicate pseudomembranous colitis, requiring immediate treatment. In such cases LOXIP must be discontinued and appropriate therapy initiated.
	Less frequent	pancreatitis
Hepatobiliary Disorders	Unknown frequency	Hepatic necrosis, very seldom progressing to hepatic failure, hepatic impairment, jaundice,

		hepatitis, increase in transaminases and bilirubin.
Skin and subcutaneous tissue disorders:	Unknown frequency	Rashes, pruritus, urticaria and photosensitivity (blisters, sensation of skin burning), erythema nodosum and erythema exsudativum multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, punctate skin haemorrhages (petechiae), haemorrhagic bullae and papules with signs of vascular involvement (vasculitis)and Acute generalised exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS).
Musculoskeletal, connective tissue and bone disorders:	Frequency unknown	Joint pain, joint swelling, general feeling of weakness (arthralgia), and myalgia (which may be of special importance in patients with myasthenia

		gravis) and tendosynovitis, cases of tendon rupture and achillotendonitis, increased muscle tone and cramping.
Renal and urinary disorders:	Frequency unknown	Crystalluria, interstitial nephritis, transient renal impairment including transient renal failure, and haematuria.
Investigations	Frequency unknown	Abnormal prothrombin level, increased amylase, Increased blood alkaline phosphatase, hyperglycaemia.

Post-marketing adverse reactions

Hyperglycaemia, hypergycaemic coma

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of acute, excessive oral over-dosage, reversible renal toxicity has been reported. Apart from routine emergency measures, it is recommended to monitor renal function and to administer magnesium- or calcium-containing antacids which reduce the absorption of oral **LOXIP**. Only a small amount of ciprofloxacin (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive.

IDENTIFICATION:

LOXIP 250 mg:

White to off-white, round shaped, film coated tablets, with a score line on one side and debossed with 'F' and '23' with a score line in between on the other side.

LOXIP 500 mg:

White to off-white, capsule shaped, film coated tablets, with a score line on one side and debossed with 'F 22' on the other side.

PRESENTATION:

LOXIP 250 mg:

Blister pack: 6's – Each carton contains 1 blister of 6 tablets each.

Tablets are packed in clear 250 microns PVC coated with 60 gsm PVdc and 25 microns printed Aluminium foil. One blister contains 6 tablets.

Blister pack: 10's – Each carton contains 1 blister of 10 tablets each.

Tablets are packed in clear 250 microns PVC coated with 60 gsm PVdc and 25 microns printed Aluminium foil. One blister contains 10 tablets.

HDPE container: 100's – Each container contains 100 tablets.

Tablets are packed in milky-white, opaque, wide mouth round 80 ml HDPE Container with 43 mm PP closure with induction sealing wad. Each container contains 100 tablets. *No dessicant is included in the container*.

LOXIP 500 mg:

Blister pack: 10's – Each carton contains 1 blister of 10 tablets each.

Tablets are packed in clear 250 microns PVC coated with 60 gsm PVdc and 25 microns printed Aluminium foil. One blister contains 10 tablets.

HDPE container: 10's- Each container contains 10 tablets. Tablets are packed in milky-white, opaque, wide mouth round 40 ml HDPE container with 33 mm PP closure with induction sealing wad. Each container contains 10 tablets. No desiccant is included in the container.

HDPE container: 100's – Each container contains 100 tablets.

Tablets are packed in milky-white, opaque, wide mouth round 140 ml HDPE Container with 43 mm PP closure with induction sealing wad. Each container contains 100 tablets. *No dessicant is included in the container*.

STORAGE INSTRUCTIONS:

Store below 30 °C.

STORE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

LOXIP 250 mg (Tablet): 41/20.1.1/1052

LOXIP 500 mg (Tablet): 41/20.1.1/1053

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration:

16 September 2014

Date of revision:

12 September 2023