SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

CIPRO UNIMED 250 mg (film-coated tablets)

CIPRO UNIMED 500 mg (film-coated tablets)

CIPRO UNIMED 750 mg (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPRO UNIMED 250:

Each film-coated tablet contains 291 mg ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin

CIPRO UNIMED 500:

Each film-coated tablet contains 582 mg ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin

CIPRO UNIMED 750:

Each film-coated tablet contains 873 mg ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin

Sugar free.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

CIPRO UNIMED 250:

White, round tablets, with breaking notch on one side

Embossment: cip 250

Diameter: 11 ± 0.2 mm

CIPRO UNIMED 500:

White, oblong tablets, with breaking notch on both sides

Embossment: cip 500

Length: 19 ± 0.2 mm

Breadth: 8.0 ± 0.2 mm

CIPRO UNIMED 750:

White, oblong tablets, with breaking notch on both sides

Embossment: cip 750

Length: 22 ± 0.2 mm

Breadth: 8.7 ± 0.2 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPRO UNIMED is indicated for the treatment of severe and/or complicated infections caused by ciprofloxacin sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated or not tolerated.

CIPRO UNIMED is not indicated/approved for the initiation of treatment (first line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to ofloxacin, unless treatment with other appropriate antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated or not tolerated.

CIPRO UNIMED is indicated for the treatment of the following bacterial infections where these infections are compliant with the indication context:

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

Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae* and *Haemophilus para-influenzae.*

Severe and/or complicated *urinary tract infections* caused by:

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

Severe and/or complicated *skin and soft tissue ~~i~~infections* caused by: *Escherichia coli; Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonasaeruginosa*, Staphyloccus aureus, Staphylococcus epidermidis, Streptococcus pyogenes.*

Severe and/or complicated *gastro-intestinal infections*:

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

Severe and/or complicated *bone infections:*

Osteomyelitis due to susceptible Gram-negative organisms.

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

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to CIPRO UNIMED.

Therapy with CIPRO UNIMED may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2 Posology and method of administration

Posology

The dosage range is 250 to 750 mg twice daily.

The duration of treatment to contain and eradicate infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings.

Use the lowest effective dose for the shortest time to contain and eradicate the infection.

In streptococcal infections the treatment must last at least 10 days because of the risk of late complications.

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

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

Severe and/or complicated *infections of the urinary tract:*

500 mg twice daily.

Severe and/or complicated *infections of the skin:*

750 mg twice daily**.**

Severe and/or complicated *Infectious diarrhoea:*

500 mg twice daily.

Severe and/or complicated *bone infections:*

750 mg twice daily. Treatment may be required for 4 – 6 weeks or longer.

Special populations

Elderly

Elderly patients should receive a dose as low as possible; this will depend on the severity of the illness and on the creatinine clearance.

Impaired renal or liver function:

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

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

Dose adjustment of CIPRO UNIMED for patients with kidney and/or liver insufficiency:

1.	Kidney insufficiency		
	1.1	$Cl_{cr} \geq 31$ ml / min / 1.73m^2 ≤ 60 mL min/1,73m^2	Max 1000 mg/day orally
	1.2	$Cl_{cr} \leq 30$ ml / min / 1.73m^2	Max 500 mg/day orally
	1.3	Impaired renal function and haemodialysis	As in 1.2 above, on dialysis days after dialysis
2.	Impaired renal function and chronic ambulatory peritoneal dialysis (CAPD):		

	2.1	Oral administration of either ciprofloxacin film coated tablet as 500 mg tablet or 2 x 250 mg tablets is indicated
	2.2	For CAPD patients with peritonitis, the recommended daily oral dose is 500 mg 4 times a day
3.	Liver function disturbances:	No dose adjustment
4.	Liver and kidney insufficiency:	As in 1.1 and 1.2 above

Method of administration

CIPRO UNIMED tablets should be swallowed whole with plenty of liquid and may be taken with or without meals.

Children and adolescents

CIPRO UNIMED is contraindicated in children less than 18 years (see sections 4.3 and 4.4).

4.3 Contraindications

- CIPRO UNIMED tablets are contraindicated in patients who have shown hypersensitivity to ciprofloxacin; any other quinolones or any of the inactive ingredients in CIPRO UNIMED (see section 6.1).
- Pregnancy and lactations (see section 4.6)

CIPRO UNIMED is contraindicated in children under 18 years. Experimental evidence indicates that, species variable reversible lesions of the cartilage of weight bearing joints has been seen in immature members of certain animal species (see section 4.4).

- Concomitant administration of CIPRO UNIMED and tizanidine (see section 4.5).
- Concomitant administration of CIPRO UNIMED and Methotrexate (see section 4.5).
- Patients with glucose-6-phosphate dehydrogenase deficiency (see section 4.4).
- Concomitant use of ciprofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to prolonged QTcF interval known to be associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with concomitant use at time intervals shorter than QT intervals usually associated with dysrhythmias.
- A history of tendon, muscle, joint, nerve, central nervous system, epilepsy or psychotic disorders especially those related to previous quinolone/fluoroquinolone use where alternative, appropriate antibiotic choices are available for treatment. (see section 4.4).
- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients (see section 4.4).
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available (see section 4.4).
- Concomitant use of fluoroquinolones with angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) in patients with moderate to severe renal impairment and in the elderly
  (see section 4.4 and 4.5).
- CIPRO UNIMED is contraindicated in patients with mitral valve and/or aortic valve regurgitation, unless no safer alternative antibiotic is available, has failed or is not well tolerated.
  A thorough cardiovascular examination, including an echocardiogram (ECG), should be performed before CIPRO UNIMED is prescribed.

4.4 Special warnings and precautions for use

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

CIPRO UNIMED should not be used in staphylococcal infections and infections involving anaerobic bacteria.

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

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

Central Nervous System:

CIPRO UNIMED should only be used where alternative appropriate therapies have failed are contraindicated or not tolerated, since these patients are endangered due to possible central nervous system side effects. CIPRO UNIMED is known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. CIPRO UNIMED should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur CIPRO UNIMED should be discontinued (see section 4.3 and 4.8).

Psychiatric effects

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

Influence on laboratory parameters/urinary sediment

Hypoglycaemia is one of the manifestations that may occur with taking CIPRO UNIMED.

Peripheral neuropathy

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

Streptococcal Infections (including Streptococcus pneumonia):

CIPRO UNIMED is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Gonorrhoea:

CIPRO UNIMED is ineffective against most strains of *Neisseria gonorrhoea*.

Syphilis:

CIPRO UNIMED is ineffective against *Treponema pallidum*

Children and adolescents:

CIPRO UNIMED is contraindicated in children less than 18 years (see sections 4.3).

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of children and adolescents. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of drug-related arthropathy by 1-year follow-up of 9.0 % and 5.7 % respectively.

Hypersensitivity:

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such a reaction occurs, CIPRO UNIMED should be discontinued and adequate medical treatment instituted.

Musculoskeletal System:

Myasthenia gravis

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

Tendinitis and tendon rupture

CIPRO UNIMED should not be used in patients with a history of tendon disease/disorder related to previous exposure quinolone or fluoroquinolone use (see section 4.3).

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with CIPRO UNIMED. This may occur within the first 48 hours of treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment (see section 4.8).

The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At any sign of tendinitis (e.g. painful swelling, inflammation), CIPRO UNIMED treatment should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g.immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Photosensitivity:

CIPRO UNIMED has been shown to cause photosensitivity reactions. Patients taking CIPRO UNIMED should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.

Cardiac disorders:

Aortic aneurysm and dissection

• There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly population. Therefore, fluoroquinolones, should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department.

QT interval prolongation

• CIPRO UNIMED has been associated with QT prolongation (see section 4.3 and 4.8).

• Concomitant use of CIPRO UNIMED with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrhythmias (e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.5) or congenital long QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia) and cardiac disease such as heart failure, myocardial infarction or bradycardia.

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

• There is some evidence of an increased risk of aortic aneurysm and/or dissection after intake of fluoroquinolones, particularly in the elderly population. Fluoroquinolones, such as CIPRO UNIMED should only be used in patients at risk if no other treatment options are available (see section 4.3). Patients at risk are patients with a positive family history of aneurysmal disease, pre-existing aortic disease and/or dissection or other risk factors or conditions predisposing to aortic aneurysm and dissection e.g. Marfan syndrome, Vascular Ehlers Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension and known atherosclerosis. In case of sudden abdominal, chest or back pain, patients should be advised to immediately go to their medical practitioner or a hospital emergency department.

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

Concomitant use of fluoroquinolones, such as CIPRO UNIMED**,** with ACE inhibitors/angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiation of treatment and monitored during treatment with fluoroquinolones and ACE inhibitors/angiotensin receptor blockers.

Dysglycaemia:

As with other quinolones, hypoglycaemia has been reported most often in diabetic patients, predominantly in the elderly population.

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with oral hypoglycaemia medicine or with insulin. Cases of hypoglycaemia coma have been reported. In diabetic patients (e.g. glibenclamide), careful monitoring of blood glucose is recommended.

Gastrointestinal System:

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

Hepatobiliary system:

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

Glucose-6-phosphate dehydrogenase deficiency:

Haemolytic reactions have been reported with CIPRO UNIMED in patients with glucose-6-phosphate dehydrogenase deficiency. CIPRO UNIMED should be avoided in these patients.

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

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

Genital tract infections:

Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone resistant *Neisseria gonorrhoea* isolates. CIPRO UNIMED should be administered for the treatment of gonococcal urethritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoea* can be excluded. For epididymo-orchitis and

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

Urinary tract infections:

Crystalluria related to the use of CIPRO UNIMED has been observed. Patients receiving CIPRO UNIMED tablets should therefore be well hydrated and excessive alkalinity of the urine should be avoided.

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

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

Intra-abdominal infections:
There are limited data on the efficacy of CIPRO UNIMED in the treatment of post-surgical intra-abdominal infections.

Infections of the bones and joints:
CIPRO UNIMED should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

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

Inhalational anthrax:

Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating medical practitioners should refer to national and/or international consensus documents regarding the treatment of anthrax.

Impaired renal function:

Since CIPRO UNIMED is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin. (see section 4.2).

Resistance:

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

Cytochrome P450:

CIPRO UNIMED inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine).

Co-administration of CIPRO UNIMED and tizanidine is contraindicated. Therefore, patients taking these medicines concomitantly with CIPRO UNIMED should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate

The concomitant use of CIPRO UNIMED with methotrexate is not recommended (see section 4.5).

Interaction with tests

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

Vision Disorders:

The association between fluoroquinolone intake and occurrence of retinal detachment has been investigated - if vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with CIPRO UNIMED (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, CIPRO UNIMED should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of CIPRO UNIMED, treatment with CIPRO UNIMED must not be restarted in this patient at any time.

4.5 Interaction with other medicines and other forms of interaction

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

Theophylline

Concurrent administration of CIPRO UNIMED 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 adverse reactions.
If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate (see section 4.4).

Other xanthine derivatives:

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

Ciclosporin:

Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Glibenclamide:

Concurrent administration of CIPRO UNIMED and glibenclamide can intensify the action of glibenclamide (hypoglycaemia). The serum glucose level should be monitored.

Probenecid:

Probenecid interferes with renal secretion of CIPRO UNIMED.
Co-administration of probenecid and CIPRO UNIMED increases the ciprofloxacin

serum concentrations.

Metoclopramide:

Metoclopramide accelerates the absorption of CIPRO UNIMED, resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Effects of other products on CIPRO UNIMED:

Drugs known to prolong QT interval:

CIPRO UNIMED should be used with caution in patients receiving medicines known to prolong QT interval (e.g. Class IA and III anti-dysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation Complex Formation:

The simultaneous administration of CIPRO UNIMED and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, CIPRO UNIMED should be administered either 1 to 2 hours before or at least 4 hours after these preparations.
The restriction does not apply to antacids belonging to the class of H_2-receptor blockers.

Food and Dairy Products:

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

Omeprazole:

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

Effects of CIPRO UNIMED on other medicinal products:

Agomelatine:

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration. Cirpofloxacin can increase the level of agomelatine in the blood.

Tizanidine:

Tizanidine must not be administered together with CIPRO UNIMED (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (Cmax increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect (see section 4.3).

Methotrexate:

Renal tubular transport of methotrexate may be inhibited by concomitant administration of CIPRO UNIMED, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Phenytoin:

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

Vitamin K antagonists

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

Duloxetine:

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

Ropinirole:

The concomitant use of ropinirole with CIPRO UNIMED, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of Cmax and AUC of ropinirole by 60 % and 84 %, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate, is recommended during and shortly after co-administration with CIPRO UNIMED (see section 4.4).

Lidocaine:

The concomitant use of lidocaine containing medicinal products with CIPRO UNIMED, a moderate inhibitor of CYP450 1A2 isozyme, reduces the clearance of intravenous lidocaine

by 22 %. A possible interaction with CIPRO UNIMED associated with side effects may occur upon concomitant administration.

Clozapine:

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

Sildenafil:

Cmax and AUC of sildenafil were increased approximately two fold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg CIPRO UNIMED. Therefore, caution should be used prescribing CIPRO UNIMED
concomitantly with sildenafil taking into consideration the risks and the benefits.

Zolpidem

Co-administration of CIPRO UNIMED may increase blood levels of zolpidem, concurrent use is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

CIPRO UNIMED should not be used during pregnancy.
In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, CIPRO UNIMED could cause damage to articular cartilage in the human immature organism / foetus.

Breastfeeding

CIPRO UNIMED is excreted in breast milk. Due to the potential risk of articular damage, CIPRO UNIMED should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

CIPRO UNIMED may impair your ability to drive or to operate machinery, especially if you use alcohol concurrently.

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

4.8 Undesirable effects

The frequency of adverse reactions reported with CIPRO UNIMED are summarised in Table 1 as per the MedDRA system organ classification (SOC).

Table 1: Tabulated list of adverse reactions		
System Organ Class	***Frequency***	**Adverse effect**
Infections and Infestations	*Less frequent*	Mycotic superinfections.
Blood and lymphatic system disorders	*Less frequent*	Eosinophilia, leukopenia, leucocytopenia granulocytopenia anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytaemia, thrombocytosis, haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening), altered prothrombin values.
Immune system disorders	*Less frequent*	Allergic reaction, angiooedema, anaphylactic reaction (e.g. facial, vascular and laryngeal oedema), anaphylactic shock (life-threatening), serum sickness-like reaction.

Endocrine disorders	*Frequency not known*	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders*	*Less frequent*	Anorexia, hyperglycaemia, hypoglycaemia (particularly in diabetic patients)
	Frequency not known	Hypoglycaemic coma
Psychiatric disorders*	*Less frequent*	Psychomotor hyperactivity, agitation, confusion, disorientation, anxiety reaction, abnormal dreams, depression, hallucinations and psychotic reactions. These may potentially culminate in suicidal ideations/thoughts or suicide attempts and completed suicide.
	Frequency not known	Mania, incl. hypomania
Nervous system disorders*	*Less frequent*	Headache, dizziness, sleep disorders/insomnia, taste disorders, par- and dysaesthesia, hypoaesthesia, tremor, seizures (incl. status epilepticus, vertigo, migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri Tiredness Nervousness Peripheral paralgesia Sweating Hallucinations

	Frequency not known	Peripheral neuropathy and polyneuropathy (see section 4.4).
Eye disorders*	*Less frequent*	Visual disturbances (e.g. diplopia), visual colour distortions
Ear and labyrinth Disorders*	*Less frequent*	Tinnitus, hearing loss / hearing impaired
Cardiac disorders	*Less frequent*	Tachycardia ventricular dysrhythmia, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged.
Vascular Disorders*	*Less frequent*	Vasodilatation, hypotension, syncope, vasculitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea (including asthmatic condition)
Gastrointestinal disorders	*Frequent*	Nausea, diarrhoea The development of severe diarrhoea may indicate pseudomembraneous colitis, requiring immediate treatment. In such cases CIPRO UNIMED tablets must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally 4 x 250 mg/day).
	Less frequent	Vomiting, gastro-intestinal and abdominal pains, dyspepsia, flatulence, Antibiotic associated colitis (very rarely with possible fatal outcome) pancreatitis

Hepato-biliary disorders	*Less frequent*	Increase in transaminases, increased bilirubin, hepatic impairment, cholestatic icterus, hepatitis, liver necrosis which may progress to life-threatening hepatic failure).
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, pruritus, urticaria, photosensitivity reactions, petechiae, erythema multiforme, erythema nodosum, Stevens Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening)
	Frequency not known	Acute generalised exanthematous pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders*	*Less frequent*	Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia, myalgia, arthritis, increased muscle tone and cramping, muscular weakness, tendonitis /Achillotenditis (e.g. painful swelling), discontinue use of CIPRO UNIMED, tendon rupture (predominantly Achilles tendon), Tendosynovitis, exacerbation of symptoms of myasthenia gravis.
Renal and urinary disorders	*Less frequent*	Renal impairment, renal failure, haematuria, crystalluria, tubulointerstitial nephritis
General disorders and administration site conditions	Less frequent	Asthenia, fever, oedema, sweating (hyperhidrosis) Impaired taste and smell, hyperglycaemia.

		Long term or repeated use of CIPRO UNIMED can lead to superinfections with resistant bacteria or fungi
Investigations	Less frequent	Increase in blood alkaline phosphatase, increased amylase Increase in transaminases or cholestatic jaundice (especially in patients with liver damage, temporary increase in urea, creatinine or hypebilirubinaemia)
	Frequency not known	International normalised ratio increased (in patients treated with Vitamin K antagonists)

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

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"**6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

Symptoms of an overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidity, to prevent crystalluria. and to administer magnesium- or calcium containing antacids which reduce the absorption of CIPRO-UNIMED tablets.

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

ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Treatment is symptomatic and supportive (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A. 20.1.1 Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Fluoroquinolones

ATC code J01MA02.

Mechanism of action

Ciprofloxacin is a synthetic, 4-quinolone derivative. *In vitro* sensitivity does not necessarily imply *in vivo* efficacy. As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Efficacy mainly depends on the relation between the maximum concentration serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the areas under the curve (AUC) and the MIC.

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV.
The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many oral active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility to ciprofloxacin.
Plasma-mediated resistance encoded by gnr-genes has been reported.

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

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

The following organisms are usually resistant:

Aerobic Gram-positive micro-organisms:

Actinomyces, *Enterococcus faecium, Listeria monocytogenes*

Aerobic Gram-negative micro-organisms:

Stenotrophomonas maltophilia

Anaerobic micro-orgamisms:

Peptostreptococcus spp., Propionibacterium acnes

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

Other micro-organisms:

Mycoplasma genitalium, Ureaplasma urealyticum, Enterococcus faecium, Nocardia asteroids.

5.2 Pharmacokinetic properties

Absorption

Ciprofloxacin plasma levels are dose-related and peak 1-2 hours after oral dosing. The absolute oral bioavailability is approximately 70 - 80 %.

Distribution

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

fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation

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

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

Elimination

Forty to fifty percent is excreted in urine as unchanged ciprofloxacin. 20 -35 % of the dose is excreted in the faeces in 5 days. Approximately 15 % of a single dose is eliminated as metabolites. Elimination is primarily renal and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 mL/minute. The elimination half-life of unchanged ciprofloxacin is 3 – 5 hours. The elimination kinetics
are linear.
Renal clearance is between 180 – 300 mL/kg/h and the total body clearance is between 480 – 600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 h.
Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism.
1 % of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline,

Sodium starch glycollate (type A),

Povidone,

Silica, colloidal anhydrous

Stearic acid,

Magnesium stearate,

Croscarmellose sodium

Film-coating:

Hypromellose,

Macrogol 6000,

Talc,

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

CIPRO UNIMED 250:

The tablets are packed into clear PVC / aluminium blister strips containing 10 tablets each.

1 (10) blister strips to be packed into a carton i.e. 10 tablets per carton

CIPRO UNIMED 500:

The tablets are packed into clear PVC / aluminium blister strips containing 10 tablets each.

1 (10) blister strips to be packed into a carton i.e. 10 tablets per carton

CIPRO UNIMED 750:

The tablets are packed into clear PVC / aluminium blister strips containing 10 tablets each.

1 (10) blister strips to be packed into a carton i.e. 10 tablets per carton

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue

Anchorville

Lenasia, 1827

South Africa

8 REGISTRATION NUMBER(S)

CIPRO UNIMED 250: 36/20.1.1/0170

CIPRO UNIMED 500: 36/20.1.1/0171

CIPRO UNIMED 750: 36/20.1.1/0172

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

Date of registration: May 2003

10 DATE OF REVISION OF THE TEXT

28 May 2024