

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Ciprofloxacin and Tinidazole Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Ciprofloxacin Hydrochloride USP equivalent to Ciprofloxacin (500 mg)

Tinidazole BP (600 mg)

3. Pharmaceutical Form

Solid Oral Dosage Form - Tablets

Orange coloured oval shaped film coated tablet plain on both side.

4. Clinical Particulars

4.1 Therapeutic indications

Ciprofloxacin and Tinidazole Tablets contains a combination of antibiotics, ciprofloxacin, belonging to the family of quinolones, and tinidazole, belonging to the family of nitroimidazole derivatives.

Ciprofloxacin and Tinidazole Tablets is indicated in infections caused by germs that are sensitive to the active ingredients and for which ciprofloxacin or Tinidazole based monotherapies are not effective, such as Chronic pouchitis and/or pouchitis resistant to the other treatment. Pelvic inflammatory disease.

4.2 Posology and method of administration

Posology

Adult

- Chronic pouchitis or those resistant to other treatment: 1 tablet of Ciprofloxacin and Tinidazole Tablets, twice a day for 4 weeks (1,000 mg of ciprofloxacin + 1,200 mg of tinidazole per day for 4 weeks).
- Upper genital infections: 1 tablet of Ciprofloxacin and Tinidazole Tablets twice a day for 7 days (500 mg of ciprofloxacin + 600 mg of tinidazole twice a day for 7 days).

Method of administration

Ciprofloxacin and Tinidazole Tablets is administered during or after a meal, preferentially. The tablets should be swallowed whole, without chewing. Ciprofloxacin and Tinidazole Tablets should not be taken with dairy products (milk, yoghurt) or fruit juices that are enriched with minerals (calcium enriched orange juice)

4.3 Contraindications

Ciprofloxacin

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients listed.
- Concomitant administration of ciprofloxacin and tizanidine.

Tinidazole

- As with other drug of similar structure, tinidazole is contraindicated in patients having, or



with a history of, blood dyscrasia, although no persistent haematological abnormalities have been noted in clinical or animal studies.

- Tinidazole should be avoided in patients with organic neurological disorders.
- Tinidazole, other 5-nitroimidazole derivatives or any of the components of this product should not be administered to patients with known hypersensitivity to the drug.
- Use of tinidazole is contraindicated during the first trimester of pregnancy and in nursing mothers.

4.4 Special warnings and special precautions for use

Ciprofloxacin

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

Ciprofloxacin 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.

Streptococcal Infections (including *Streptococcus pneumoniae*)

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

Genital tract infections

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

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

Urinary tract infections

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infection – varies across the European Union. 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 woman 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 ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea

The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of bones and joints

Ciprofloxacin should be used in combination with the other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax

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

Paediatric population

The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. 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 suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day + 42 of 7.2 % and 4.6 %. Respectively, an incident of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

Broncho-pulmonary infections in cystic fibrosis

Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation. Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections

Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use. The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reactions occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.



Musculoskeletal system

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Photosensitivity

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

Central nervous system

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizures. If seizures occur ciprofloxacin should be discontinued. Psychiatric reactions may occur even after the first administration of ciprofloxacin. 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, ciprofloxacin should be discontinued. Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.

Cardiac disorders

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Congenital long QT syndrome.
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic).
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia).
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Elderly patients and women may be more sensitive to QTc-prolonging medication. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.

Hyperglycemia

As with other quinolones, hypoglycemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, 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 antibiotic-associated colitis (life-threatening with possible fatal outcomes), requiring immediate treatment. In such cases, ciprofloxacin should immediately be discontinued in this situation.

Renal and urinary system

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

Impaired renal function

Since ciprofloxacin 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.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (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), the treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance

During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be 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

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizandine, duloxetine). Co-administration of ciprofloxacin and tizandine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentration (e.g. of theophylline) may be necessary.

Methotrexate

The concomitant use of ciprofloxacin with methotrexate is not recommended.

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 ciprofloxacin.



Tinidazole

As with related compounds, alcoholic beverages should be avoided during tinidazole 600 mg tablets therapy because of the possibility of a disulfiram-like reaction (flushing, abdominal cramps, vomiting, tachycardia). Alcohol should be avoided until 72 hours after discontinuing tinidazole 600 mg tablets.

Drugs of similar chemical structure have also produced various neurological disturbances such as dizziness, vertigo, incoordination and ataxia. If during therapy with tinidazole 600 mg tablets, abnormal neurological signs develop, therapy should be discontinued.

Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although carcinogenicity data is not available for tinidazole, the two drugs are structurally related and therefore there is a potential for similar biological effects. Mutagenicity results with tinidazole for longer treatment (positive and negative). The use of tinidazole for longer treatment than usually required should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction:

Effects of other products on ciprofloxacin:

Drugs known to prolong QT interval

Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations.

The restriction does not apply to antacids belonging to the class of H₂ 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 ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole

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

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin. In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} 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.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

Other xanthine derivatives

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

Phenytoin

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

Cyclosporin

A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists

Simultaneous administration of ciprofloxacin 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 ciprofloxacin 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 ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Duloxetine

In clinical studies, it was demonstrated that concomitant use of duloxetine with strong



inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} 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 ciprofloxacin.

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

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.

Zolpidem

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

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Tinidazole

Alcohol

Concurrent use of tinidazole and alcohol may produce a disulfiram-like reaction and should be avoided.



Anticoagulant

Drugs of similar chemical structure have been shown to potentiate the effects of oral anticoagulants.

Prothrombin time should be closely monitored and adjustments to the dose of the anticoagulant should be made as necessary.

4.6 Fertility, pregnancy and lactation:

Ciprofloxacin

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus. As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Breast-feeding

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

Tinidazole

Pregnancy

Fertility studies in rats receiving 100 mg and 300 mg tinidazole/kg had no effect on fertility, adult and pup weight, gestation, viability or lactation. There was a slight, not significant, increase in resorption rate at the 300 mg/kg dose.

Tinidazole crosses the placental barrier. Since the effect of compounds of this class on foetal development are unknown, the use of tinidazole during the first trimester is contraindicated. There is no evidence that tinidazole 600 mg tablets is harmful during the latter stages of pregnancy, but its use during the second and third trimesters requires that the potential benefits be weighed against possible hazards to mother or foetus.

Breast-feeding

Tinidazole is excreted in breast milk. Tinidazole may continue to appear in breast milk for more than 72 hours after administration. Women should not nurse until at least 3 days after having discontinued taking tinidazole 600 mg tablets

4.7 Effects on ability to drive and use machines

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

Tinidazole

No special precautions should be necessary. However, drugs of similar chemical structure, including tinidazole 600 mg tablets, have been associated with various neurological disturbances such as dizziness, vertigo, ataxia, peripheral neuropathy (paraesthesia, sensory disturbances, hypoaesthesia) and rarely convulsions. If any abnormal neurological signs

develop during tinidazole 600 mg tablet therapy, the drug should be discontinued.

4.8 Undesirable effects

Classification of expected frequencies Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin sorted by categories of frequencies are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

Infections and infestations

Uncommon : mycotic super-infections.

Rare : antibiotic associated colitid (very rarely possible fatal outcome)

Blood and lymphatic system disorders

Uncommon : eosinophilia.

Rare : leukopenia, anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytaemia.

Very rare : haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening).

Immune system disorders

Rare : allergic reaction, allergic oedema/angioedema

Very rare : anaphylactic reaction, anaphylactic shock (life-threatening) serum-sickness-like reaction.

Metabolism and nutrition disorders

Uncommon : decreased appetite.

Rare : hyperglycaemia, hypoglycaemia.

Psychiatric disorders

Uncommon : psychomotor hyperactivity/agitation.

Rare : confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide, hallucinations.

Very rare : psychotic reactions (potentially culminating in suicidal ideations. thoughts or suicide attempts and completed suicide).

Nervous system disorders

Uncommon : headache, dizziness, sleep disorders, taste disorders.

Rare : par- and dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo.

Very rare : migraine, disturbed coordination, Gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri.

Frequency not known : peripheral neuropathy and polyneuropathy.

Eye disorders

Rare : visual disturbances (e.g. diplopia).

Very rare : visual colour distortion.

Ear and labyrinth disorders

Rare : tinnitus, hearing loss/hearing impaires.

Cardiac disorders

Rare : tachycardia.

Frequency not known : ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged

Vascular disorders

Rare : vasodilation, hypotension, syncope.

Very rare : vasculitis.

Respiratory, thoracic and mediastinal disorders

Rare : dyspnoea (including asthmatic condition).

Gastro-intestinal disorders

Common : nausea, diarrhoea.

Uncommon : vomiting, gastro-intestinal and abdominal pains, dyspepsia, flatulence.

Very rare : pancreatitis.

Hepatobiliary disorders

Uncommon : increase trasaminases, increased bilirubin.

Rare : hepatic impairment, cholestatic icterus, hepatitis.

Skin and subcutaneous tissues disorders

Uncommon : rash, pruritus, urticaria.

Rare : photosensitivity reactions

Very rare : petechiae, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening).

Frequency not known : acute generalised exanthematous pustolosis (AGEP).

Musculo-skeletal and connective tissue disorders

Uncommon : musculo-skeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia.

Rare : myalgia, arthritis, increased muscle tone and cramping.

Very rare : muscular weakness, tendinitis, tendon ruptur (predominantly achilles Tendon), exacerbation of symptoms of myasthenia gravis.

Renal and urinary disorders

Uncommon : renal impairment.

Rare : renal failure, haematuria, crystalluria, tubulointerstitial nephritis.

General disorders and administration site conditions

Uncommon : asthenia, fever.

Very rare : oedema, sweating (hyperhidrosis).

Investigation

Uncommon : increase in blood alkaline phosphatase.

Rare : increased amylase.

Frequency not known : international normalised ratio increased (in patients treated with vitamine K antagonists).

Paediatric population

The incidence of arthropathy, mentioned above, is referring to data collectioned in studies with adults. In children, arthropathy is reported to occur commonly.

Tinidazole

Reported side effects have generally been infrequent, mild and self-limiting.

Automatic nervous system: flushing.

Body as a whole: fever, tiredness.

Central and peripheral nervous system: ataxia, convulsion (rarely), dizziness, headache, hypoaesthesia, parathesia, peripheral neuropathy, sensory disturbances, vertigo.

Gastrointestinal: abdominal pain, anorexia, diarrhoea, durry tongue, glossitis, nausea, stomatis, vomiting.

Haematopoietic: transient leukopenia.

Skin/appendages: hypersensitivity reactions, occasionally sever may occur in rare cases in the form of the skin rash, pruritus, urticaria, and angineurotic oedema.

Special senses: metallic taste.

Urinary system: dark urine.

4.9 Overdose

An overdose of 12g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon it is recommended to monitor renal function, including urinary pH and acidify, if



required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

Tinidazole

In acute animal studies with mice and rats, the LD50 for mice was > 3600 mg/kg and > 2300 mg/kg for oral and intraperitoneal administration respectively. For rats, the LD50 was > 2000 mg/kg for both oral and intraperitoneal administration.

Signs and symptoms of overdosage: there are no reported overdoses in humans with tinidazole 600 mg tablets.

Treatment for overdosage: there is no specific antidote for treatment of overdosage with tinidazole.

Treatment is symptomatic and supportive. Gastric lavage may be useful. Tinidazole is easily dialyzable

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of antibacterials, ciprofloxacin and tinidazole, ATC code: J01RA11

Mechanism of action:

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.

Pharmacokinetic /Pharmacodynamic relationship:

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

Mechanism of resistance:

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 or all 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.

Plasmid-mediated resistance encoded by *qnr*-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	Susceptible	Resistant
Enterobacteriaceae	$S \leq 0.5 \text{ mg/L}$	$R > 1 \text{ mg/L}$
<i>Pseudomonas</i> spp.	$S \leq 0.5 \text{ mg/L}$	$R > 1 \text{ mg/L}$
<i>Acinetobacter</i> spp.	$S \leq 1 \text{ mg/L}$	$R > 1 \text{ mg/L}$
<i>Staphylococcus</i> spp. ¹	$S \leq 1 \text{ mg/L}$	$R > 1 \text{ mg/L}$
<i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i>	$S \leq 0.5 \text{ mg/L}$	$R > 0.5 \text{ mg/L}$
<i>Neisseria gonorrhoeae</i>	$S \leq 0.03 \text{ mg/L}$	$R > 0.06 \text{ mg/L}$
<i>Neisseria meningitidis</i>	$S \leq 0.03 \text{ mg/L}$	$R > 0.06 \text{ mg/L}$
Non-species-related breakpoints*	$S \leq 0.5 \text{ mg/L}$	$R > 1 \text{ mg/L}$

1 *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility.

Commonly Susceptible Species	Species For Which Aquired Resistance May Be A Problem	Inherently Resistant Organisms
Aerobic Gram-positive micro-organisms <i>Bacillus anthracis</i> (1)	Anaerobic Gram-positive microorganisms <i>Enterococcus faecalis</i> (*) <i>Staphylococcus</i> spp.*(2)	Aerobic Gram-positive microorganisms <i>Actinomyces</i> <i>Enterococcus faecium</i> <i>Listeria monocytogenes</i>
Aerobic Gram-negative	Aerobic Gram-negative	Aerobic Gram-negative

micro-organisms Aeromonas spp. Brucella spp. Citrobacter koseri Francisella tularensis Haemophilus ducreyi Haemophilus influenzae* Legionella spp. Moraxella catarrhalis* Neisseria meningitidis Pasteurella spp. Salmonella spp.* Shigella spp.* Vibrio spp. Yersinia pestis	microorganisms Acinetobacter baumannii+ Burkholderia cepacia+* Citrobacter freundii* Enterobacter aerogenes Enterobacter cloacae* Escherichia coli Klebsella oxytoca Klebsella pneumoniae* Morganella morganii* Neisseria gonorrhoeae* Proteus mirabilis* Proteus vulgaris* Providencia spp. Pseudomonas aeruginosa* Pseudomonas fluorescens Serratia marcescens*	microorganisms Stenotrophomonas maltophilia
Anaerobic micro-organisms Mobiluncus	Anaerobic micro-organisms Peptostreptococcus spp. Propionibacterium acnes	Anaerobic micro-organisms Excepted as listed above
Other micro-organisms Chlamydia trachomatis (\$) Chlamydia pneumoniae (\$) Mycoplasma hominis (\$) Mycoplasma pneumoniae (\$)		Other micro-organisms Mycoplasma genitalium Ureaplasma urealyticum
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate $\geq 50\%$ in one or more EU countries (\$): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on in-vitro susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax. (2):Methicillin-resistant S. aureus very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.		

Tinidazole

Tinidazole is active against both protozoa and obligate anaerobic bacteria. The activity against protozoa involves Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia. The mode of action of tinidazole against anaerobic bacteria and protozoa involves penetration

of the drug into the cell of the micro-organism and subsequent damage of DNA strands or inhibition of their synthesis.

Tinidazole is active against *Helicobacter pylori*, *Gardnerella vaginalis* and most anaerobic bacteria including *Bacteroides fragilis*, *Bacteroides melaninogenicus*, *Bacteroides* spp., *Clostridium* spp., *Eubacterium* spp., *Fusobacterium* spp., *Peptococcus* spp., *Peptostreptococcus* spp. and *Veillonella* spp.

Helicobacter pylori (*H. pylori*) is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95 % and 80 % of patients respectively are infected with this agent. *H. pylori* is also implicated as a major contributing factor in the development of gastritis and ulcer recurrence in such patients. Evidence suggests a causative link between *H. pylori* and gastric carcinoma.

Clinical evidence has shown that the combination of tinidazole with omeprazole and clarithromycin eradicates 91-96 % of *H. pylori* isolates.

Various different *H. pylori* eradication regimens have shown that eradication of *H. pylori* heals ulcers and reduces the risk of ulcer recurrence.

5.2 Pharmacokinetic properties:

Ciprofloxacin

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.

Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.

The absolute bioavailability is approximately 70-80%.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin 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

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

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.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

Tinidazole

Tinidazole is rapidly and completely absorbed following oral administration. In studies with healthy volunteers receiving 2 g tinidazole orally, peak serum levels of 40-51 microorganisms/mL were achieved within two hours and decreased to between 11-19 microorganisms/mL at 24 hours. Healthy volunteers who received 800 mg and 1.6 g tinidazole IV over 10 – 15 minutes achieved peak plasma concentrations that ranged from 14 to 21 mg/mL for the 800 mg dose and averaged 32 mg/mL for the 1.6 dose. At 24 hours postinfusion, plasma levels of tinidazole decreased to 4-5 mg/mL and 8.6 mg/mL



respectively, justifying once daily dosing. Plasma levels decline slowly and tinidazole can be detected in plasma at concentration of up to 1 microorganism/mL at 72 hours after oral administration. The plasma elimination half-life for tinidazole is between 12-14 hours.

Tinidazole is widely distributed in all body tissues and also crosses the blood brain barrier, obtaining clinically effective concentrations in all tissues. The apparent volume of distribution is about 50 L. About 12 % of plasma tinidazole is bound to plasma protein.

Tinidazole is excreted by the liver and kidneys. Studies in healthy patients have shown that over 5 days, 60-65 % of an administered dose is excreted by the kidneys with 20-25 % of the administered dose excreted as unchanged tinidazole. Up to 5 % of the administered dose is excreted in the faeces.

Studies in patients with renal failure (creatinine clearance < 22 mL/min) indicate that there is no statistically significant change in tinidazole pharmacokinetic parameters in these patients.

5.3 Preclinical safety data:

Ciprofloxacin

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin in-vitro and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

Tinidazole:

Tinidazole has been shown to be mutagenic in some bacterial strains tested in vitro (with and without metabolic activation). Tinidazole was negative for mutagenicity in a mammalian cell culture system utilising Chinese hamster lung V79 cells (HGPRT test system) and negative for genotoxicity assay. Tinidazole was positive for in vivo genotoxicity in the mouse micronucleus assay.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose pH 101 BP

Colloidal Silicon Dioxide BP

Sodium lauryl sulphate BP



Starch BP
Polyvinyl Pyrrolidone BP
Magnesium stearate BP
Croscarmellose Sodium BP
Purified talc BP
Microcrystalline Cellulose pH 102 BP
Hydroxy Propyl Methyl Cellulose (E - 15 cps) BP
Propylene Glycol BP
Instacoat Aqua Orange IHS (Hypromellose, Polyethylene Glycol, Polyvinyl Alcohol, Talc, Calcium Carbonate, Lake sunset yellow.)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry place. Protect from light and moisture.

6.5 Nature and contents of container

10 x 1 x 10's Pack

10 Tablets are packed in Alu – Alu Blister.

Such one blister is packed in Monocarton.

Such 10 monocartons are packed in an outer carton with a printed leaflet.

6.6 Special precautions for disposal and other handling

None

7. Manufacturer

Emil Pharmaceutical Industries Pvt. Ltd.

Plant Address:

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