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1. Name of the medicinal product

Zoopro 500 mg film-coated tablets.

2. Qualitative and quantitative composition

Zoopro 500.00 mg (as Ciprofloxacin hydrochloride).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets.

White colored, oblong shaped, biconvex film-coated tablets, plain on one side and break line on other side.

4. Clinical particulars

4.1 Therapeutic indications

Zoopro 500mg film-coated tablets are indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to Zoopro (ciprofloxacin) before commencing therapy.

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

Adults

• Lower respiratory tract infections due to Gram-negative bacteria

- acute exacerbations of chronic obstructive pulmonary disease

- Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

- pneumonia

• Chronic suppurative otitis media

• Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria

• Uncomplicated acute cystitis

In uncomplicated acute cystitis Zoopro film-coated tablets should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

• Acute pyelonephritis

• Complicated urinary tract infections

• Bacterial prostatitis

• Genital tract infections

- gonococcal urethritis and cervicitis due to susceptible Neisseria gonorrhoeae

- epididymis-orchitis including cases due to Neisseria gonorrhoeae

- pelvic inflammatory disease including infections due to Neisseria gonorrhoeae

• Infections of the gastro-intestinal tract (e.g. travelers' diarrhea)

• Intra-abdominal infections

• Infections of the skin and soft tissue caused by Gram-negative bacteria

• Infections of the bones and joints

• Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Zoopro may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Children and adolescents

• Broncho-pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis

• Complicated urinary tract infections and acute pyelonephritis

• Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Zoopro may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Posology

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to Zoopro of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course

Treatment of infections due to certain bacteria (e.g. Pseudomonas aeruginosa, Acinetobacter or Staphylococci) may require higher Zoopro doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications

Daily dose in mg

Total duration of treatment

(potentially including initial parenteral treatment with Zoopro)

Infections of the lower respiratory tract

500 mg twice daily to 750 mg twice daily

7 to 14 days

Infections of the upper respiratory tract

Acute exacerbation of chronic sinusitis

500 mg twice daily to 750 mg twice daily

7 to 14 days

Chronic suppurative otitis media

500 mg twice daily to 750 mg twice daily

7 to 14 days

Urinary tract infections

(see section 4.4)

Uncomplicated cystitis

250 mg twice daily to 500 mg twice daily

3 days

In pre-menopausal women, 500 mg single dose may be used

Complicated cystitis, Acute uncomplicated pyelonephritis

500 mg twice daily

7 days

Acute complicated pyelonephritis

500 mg twice daily to 750 mg twice daily

at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)

Bacterial prostatitis

500 mg twice daily to 750 mg twice daily

2 to 4 weeks (acute) to 4 to 6 weeks (chronic)

Genital tract infections

Gonococcal urethritis and cervicitis due to susceptible Neisseria gonorrhoeae

500 mg as a single dose

1 day (single dose)

Epididymis-orchitis and pelvic inflammatory diseases

500 mg twice daily to 750 mg twice daily

at least 14 days

Infections of the gastro-intestinal tract and intra-abdominal infections

Diarrhea caused by bacterial pathogens including Shigella spp. other than Shigella dysenteries type 1 and empirical treatment of severe traveler's diarrhea

500 mg twice daily

1 day

Diarrhea caused by Shigella dysenteries type 1

500 mg twice daily

5 days

Diarrhea caused by Vibrio cholerae

500 mg twice daily

3 days

Typhoid fever

500 mg twice daily

7 days

Intra-abdominal infections due to Gram-negative bacteria

500 mg twice daily to 750 mg twice daily

5 to 14 days

Infections of the skin and soft tissue

500 mg twice daily to 750 mg twice daily

7 to 14 days

Bone and joint infections

500 mg twice daily to 750 mg twice daily

max. of 3 months

Neutropenic patients with fever that is suspected to be due to a bacterial infection.

500 mg twice daily to 750 mg twice daily

Therapy should be continued over the entire period of neutropenia

Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.

500 mg twice daily

60 days from the confirmation of Bacillus anthracis exposure

Pediatric population

Indications

Daily dose in mg

Total duration of treatment (potentially including initial parenteral treatment with Zoopro)

Broncho pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa

20 mg/kg body weight twice daily with a maximum of 750 mg per dose.

10 to 14 days

Complicated urinary tract infections and acute pyelonephritis

10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.

10 to 21 days

Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.

10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.

60 days from the confirmation of Bacillus anthracis exposure

Other severe infections

20 mg/kg body weight twice daily with a maximum of 750 mg per dose.

According to the type of infections

Elderly patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Patients with renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m^2]

Serum Creatinine [µmol/L]

Oral Dose [mg]

> 60

< 124

See Usual Dosage.

30-60

124 to 168

250-500 mg every 12 h

< 30

> 169

250-500 mg every 24 h

Patients on haemodialysis

> 169

250-500 mg every 24 h (after dialysis)

Patients on peritoneal dialysis

> 169

250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. Zoopro tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous Zoopro until a switch to oral administration is possible.

4.3 Contraindications

• Hypersensitivity to the active substance, to other quinolones or to any of the excipients listed in section 6.1.

• Concomitant administration of Zoopro and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

The use of Zoopro should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8).

Treatment of these patients with Zoopro should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

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. Zoopro should be discontinued immediately at the first signs or symptoms of any adverse reaction and patients should be advised to contact their prescriber for advice.

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

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

Streptococcal Infections (including Streptococcus pneumonia)

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

Genital tract infections

Gonococcal uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory disease may be caused by fluoroquinolones-resistant Neisseria gonorrhoeae isolates.

Therefore, Zoopro should be administered for the treatment of gonococcal uretritis or cervicitis only if Zoopro-resistant Neisseria gonorrhoeae can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical Zoopro should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless Zoopro-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 infections – 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 Zoopro 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 Zoopro in the treatment of post-surgical intra-abdominal infections.

Travelers' diarrhea

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

Infections of the bones and joints

Zoopro should be used in combination with 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.

Pediatric population

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

Zoopro has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomized double-blind study on Zoopro use in children (Zoopro: 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 incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase 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 (see section 4.8).

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

Zoopro treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based in 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 guidelines, 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 Zoopro use.

The use of Zoopro 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 (see section 4.8) and may be life-threatening. If such reaction occurs, Zoopro should be discontinued and an adequate medical treatment required.

Tendinitis and tendon rupture. Zoopro 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, Zoopro 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 microbiological data may justify the use of Zoopro.

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. 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 the first sign of tendinitis (e.g. painful swelling, inflammation), the treatment with Zoopro should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur

Zoopro should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated (see section 4.8).

Photosensitivity

Zoopro has been shown to cause photosensitivity reactions. Patients taking Zoopro should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System

Zoopro like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Zoopro should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur Zoopro should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of Zoopro. 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, Zoopro should be discontinued.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paranesthesia, hypesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and

fluoroquinolones. Patients under treatment with Zoopro 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).

Cardiac disorders

Caution should be taken when using fluoroquinolones including Zoopro, 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 anti-arrhythmic, tricyclic antidepressants, macrolides, antipsychotics)

• uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesaemia)

• cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

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

(See section 4.2 Elderly patients, section 4.5, section 4.8 and section 4.9).

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

• for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally

• for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally

• for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

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

Patients should be advised to seek immediate medical attention in case of acute dyspnea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Dysglycaemia

As with other quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Gastrointestinal System

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

Renal and urinary system

Crystalluria related to the use of Zoopro has been reported (see section 4.8). Patients receiving Zoopro should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since Zoopro is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of Zoopro.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with Zoopro (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.

Glucose-6-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with Zoopro in patients with glucose-6-phosphate dehydrogenase deficiency. Zoopro 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 Zoopro bacteria that demonstrate resistance to Zoopro may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for Zoopro-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by Staphylococcus and Pseudominas species.

Cytochrome P450

Zoopro inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of Zoopro and tizanidine is contraindicated. Therefore, patients taking these substances concomitantly with Zoopro 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 Zoopro with methotrexate is not recommended (see section 4.5).

Interaction with tests

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

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other products on Zoopro

Drugs known to prolong QT interval

Zoopro like other fluoroquinolones should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation Complex Formation

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

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 Zoopro should be avoided because absorption of Zoopro may be reduced.

Probenecid

Probenecid interferes with renal secretion of Zoopro. Coadministration of probenecid and Zoopro increases Zoopro serum concentrations.

Metoclopramide

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

Omeprazole

Concomitant administration of Zoopro and omeprazole containing medicinal products results in a slight reduction of Cmax and AUC of Zoopro.

Effects of Zoopro on other medicinal products:

Tizanidine

Tizanidine must not be administered together with Zoopro (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 Zoopro. 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 Zoopro, 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).

Theophylline

Concurrent administration of Zoopro 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 (see section 4.4).

Other xanthine derivatives

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

Phenytoin

Simultaneous administration of Zoopro 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 Zoopro 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 Zoopro with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of Zoopro to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after

coadministration of Zoopro 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 Cmax of duloxetine. Although no clinical data are available on a possible interaction with Zoopro, similar effects can be expected upon concomitant administration (see section 4.4).

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with Zoopro, 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 coadministration with Zoopro (see section 4.4).

Lidocaine

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

Clozapine

Following concomitant administration of 250 mg Zoopro 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 Zoopro are advised (see section 4.4).

Sildenafil

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

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 Zoopro, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration ('Cytochrome P450' in section 'Special warnings and precautions for use).

Zolpidem

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The data that are available on administration of Zoopro to pregnant women indicates no malformative or feto/neonatal toxicity of Zoopro. 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 (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Zoopro during pregnancy.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

ADRs derived from clinical studies and post-marketing surveillance with Zoopro (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of Zoopro.

System Organ Class

Common

≥ 1/100 to < 1/10

Uncommon

≥ 1/1,000 to < 1/100

Rare

≥ 1/10,000 to < 1/1,000

Very Rare

< 1/10,000

Frequency not known (cannot be estimated from available data)

Infections and Infestations

Mycotic superinfections

Blood and Lymphatic System Disorders

Eosinophilia

Leukopenia

Anaemia

Neutropenia

Leukocytosis

Thrombocytopenia

Thrombocytaemia

Haemolytic anaemia

Agranulocytosis

Pancytopenia (life threatening)

Bone marrow depression (life threatening)

Immune System Disorders

Allergic reaction

Allergic oedema/ angiooedema

Anaphylactic reaction

Anaphylactic shock (life threatening)

(see section 4.4)

Serum sickness like reaction

Endocrine disorders

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Metabolism and Nutrition Disorders

Decreased appetite

Hyperglycaemia

Hypoglycaemia (see section 4.4)

Hypoglycaemic coma (see section 4.4)

Psychiatric disorders*

Psychomotor hyperactivity/ agitation

Confusion and disorientation

Anxiety reaction

Abnormal dreams

Depression

(potentially culminating in suicidal ideation/thoughts or suicide attempts and completed suicide) (see section 4.4)

Hallucination

Psychotic reactions (potentially culminating in suicidal ideations/thought or suicide attempts and completed suicide) (see section 4.4)

Mania, hypomania

Nervous System Disorders*

Headache

Dizziness

Sleep disorders

Taste disorders

Par- and Dysaesthesia

Hypoaesthesia

Tremor

Seizures (including status epliepticus see section 4.4)

Vertigo

Migraine

Disturbed coordination

Gait disturbance

Olfactory nerve disorders

Intracranial hypertension and psuedotumor cerebri

Peripheral neuropathy and polyneuropathy (see section 4.4)

Eye Disorders*

Visual disturbances

Visual colour distortions

Ear and Labyrinth Disorders*

Tinnitus

Hearing loss/ Hearing impaired

Cardiac Disorders**

Tachycardia

Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation) ECG QT prolonged (see section 4.4 and 4.9)

Vascular Disorders**

Vasodilatation

Hypotension

Syncope

Vasculitis

Respiratory, Thoracic and Mediastinal Disorders

Dyspnoea (including asthmatic condition)

Gastrointestinal Disorders

Nausea

Diarrhoea

Vomiting

Gastrointestinal and abdominal pains

Dyspepsia

Flatulence

Antibiotic associated diarrhoea including pseudomembraneous colitis (very rarely with possible fatal outcome) (see section 4.4)

Pancreatitis

Hepatobiliary Disorders

Increase in transaminases

Increased bilirubin

Hepatic impairment

Cholestatic icterus

Hepatitis

Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)

Skin and Subcutaneous Tissue Disorders

Rash

Pruritus

Urticaria

Photosensitivity reactions (see section 4.4)

Petechiae

Erythema multiforme

Erythema nodosum

Stevens-Johnson syndrome (potentially life threatening)

Toxic epidermal necrolysis (potentially life threatening)

Acute generalised exanthematous pustulosis (AGEP),

DRESS

Musculoskeletal, Connective Tissue and Bone Disorders*

Musculoskeletal pain (e.g. extremity pain, back pain, chest pain)

Arthralgia

Myalgia

Arthritis

Increased muscle tone and cramping

Muscular weakness

Tendinitis

Tendon rupture

(predominantly Achilles tendon) (see section 4.4)

Exacerbation of symptoms of myasthenia gravis (see section 4.4)

Renal and Urinary Disorders

Renal impairment

Renal failure

Haematuria

Crystalluria (see section 4.4)

Tubulointerstitial nephritis

General Disorders and Administration Site Conditions*

Asthenia

Fever

Oedema

Sweating

(hyperhidrosis)

Investigations

Increase in blood alkaline phosphatase

Increased amylase

International normalised ratio increased (in patients treated with Vitamin K antagonists)

*Very rare case 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 rapture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment in 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).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Paediatric patients

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal products is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 of overdose may include dizziness, tremor, headaches, 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 Zoopro in overdoses.

Only a small quantity of Zoopro (<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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones

ATC code J01M A02

Mechanism of Action:

As a fluoroquinolones antibacterial agent, the bactericidal action of Zoopro results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) and the minimum inhibitory concentration (MIC) of Zoopro for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:

In-vitro resistance to Zoopro can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between Zoopro 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 the susceptibility to fluoroquinolones, which depends on 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 Zoopro.

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

Enterobacteria

S ≤ 0.5 mg/L

R > 1 mg/L

Pseudomonas

S ≤ 0.5 mg/L

R > 1 mg/L

Acinetobacter

S ≤ 1 mg/L

R > 1 mg/L

Staphylococcus spp.1

S ≤ 1 mg/L

R > 1 mg/L

Haemophilus influenzae and Moraxella catarrhalis

S ≤ 0.5 mg/L

R > 0.5 mg/L

Neisseria gonorrhoeae

S ≤ 0.03 mg/L

R > 0.06 mg/L

Neisseria meningitidis

S ≤ 0.03 mg/L

R > 0.06 mg/L

Non-species-related breakpoints*

S ≤ 0.5 mg/L

R > 1 mg/L

1 Staphylococcus spp. - breakpoints for Zoopro 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 Zoopro susceptibility (for Streptococcus species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES

Aerobic Gram-positive micro-organisms

Bacillus anthracis (1)

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

Anaerobic micro-organisms

Mobiluncus

Other micro-organisms

Chlamydia trachomatis ($)

Chlamydia pneumoniae ($)

Mycoplasma hominis ($)

Mycoplasma pneumoniae ($)

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive micro-organisms

Enterococcus faecalis ($)

Staphylococcus spp. *(2)

Aerobic Gram-negative microorganisms

Acinetobacter baumannii+

Burkholderia cepacia+*

Campylobacter spp.+*

Citrobacter freundii*

Enterobacter aerogenes

Enterobacter cloacae*

Escherichia coli*

Klebsiella oxytoca

Klebsiella pneumoniae*

Morganella morganii*

Neisseria gonorrhoeae*

Proteus mirabilis*

Proteus vulgaris*

Providencia spp.

Pseudomonas aeruginosa*

Pseudomonas fluorescens

Serratia marcescens*

Anaerobic micro-organisms

Peptostreptococcus spp.

Propionibacterium acnes

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-positive micro-organisms

Actinomyces

Enteroccus faecium

Listeria monocytogenes

Aerobic Gram-negative micro-organisms

Stenotrophomonas maltophilia

Anaerobic micro-organisms

Excepted as listed above

Other micro-organisms

Mycoplasma genitalium

Ureaplasma urealitycum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

+ Resistance rate ≥ 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 Zoopro 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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of single doses of 250 mg, 500 mg and 750 mg of Zoopro tablets, Zoopro 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 (Cmax) between 0.56 and 3.7 mg/L. Serum concentration 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 400mg Zoopro given over 60 minutes every 12 hours.

Distribution

Protein binding of Zoopro is low (20-30%). Zoopro 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. Zoopro 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: desethyleneZoopro (M 1), sulphoZoopro (M 2), oxoZoopro (M 3) and formylZoopro (M 4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound. Zoopro is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Zoopro 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 Zoopro (% of dose)

Oral Administration

Urine

Faeces

Zoopro

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. Zoopro undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of Zoopro up to 12 h.

Non-renal clearance of Zoopro is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Zoopro is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

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

In 10 children with severe sepsis Cmax 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%.

5.3 Preclinical safety data

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

Articular tolerability:

As reported for other gyrase inhibitors, Zoopro 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, Zoopro caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. Pharmaceutical particulars

6.1 List of excipients

For the Core:

Cellulose microcrystalline

Sodium Starch Glycolate

Starch Maize

Silica Colloidal anhydrous

Magnesium stearate.

For the Film-Coating:

Opadry OY 58900 White:

Hydroxypropyl Methylcellulose (Hypromellose)

Titanium dioxide (E171)

Macrogol 400.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years (24 months)

6.4 Special precautions for storage

Do not store above 25°C.

Keep in the original container.

6.5 Nature and contents of container

Alu/Alu pack of 10 tablets

6.6 Special precautions for disposal and other handling

None.

7. APPLICANT/MANUFACTURER

Manufactured in India for:

ZOOMOTA HEALTHCARE LIMITED MEDICEF PHARMA

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