SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINE

Glacipro 500 film-coated tablet

2. QUALTITATIVE AND QUANTITATIVE COMPOSTION

Each film-coated tablet contains,
Ciprofloxacin hydrochloride……500mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

• there is resistance to other first-line antibiotics recommended for the infection;

• other first-line antibiotics are contraindicated in an individual patient;

• other first-line antibiotics have caused side effects requiring treatment to be stopped;

• treatment with other first-line antibiotics has failed.

Ciprofloxacin 500 mg 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 ciprofloxacin before commencing therapy.

Adults

• Lower respiratory tract infections due to Gram-negative bacteria

o exacerbations of chronic obstructive pulmonary disease. Ciprofloxacin 500 mg 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.

o broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

o pneumonia

• Chronic suppurative otitis media

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

• Uncomplicated acute cystitis. Ciprofloxacin 500 mg 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

o gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*

o epididymo-orchitis including cases due susceptible to *Neisseria gonorrhoeae*

o pelvic inflammatory disease including cases due susceptible to *Neisseria gonorrhoeae*

• Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)

• Intra-abdominal infections

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

• Malignant external otitis

• Infections of the bones and joints

• Prophylaxis of invasive infections due to *Neisseria meningitidis*

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

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to 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)

Ciprofloxacin 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).

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

4.2. Posology and method of administration

Posology
Glacipro tablets should not be crushed or divided for intake and should be swallowed whole with plenty of liquid with or without meals.
The duration of treatment depends on the severity of the illness and on the clinical bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms

In acute uncomplicated urinary tract infections (acute cystitis) where treatment with other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated: 500 mg once daily for 3 days

In severe and/or complicated urinary tract infections or acute uncomplicated pyelonephritis where other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated: 1 000 mg once daily for 7 - 14 days. In severe and/or complicated bacterial diarrhoea where other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated: 1 000 mg once daily for up to 7 days.

Special populations
Geriatric patients (> 65 years)
Elderly patients should receive a dose as low as possible depending on the severity of their illness and on the creatinine clearance (see Patients with renal and hepatic impairment under section 4.2).

Patients with renal and hepatic impairment
Patients with renal impairment
No dose adjustment is required for patients with mild to severe renal impairment (i.e. where creatinine clearance is equal or is less than 30 mL /min/1,73m² or where the serum creatinine concentration is equal or higher than 0,17 mmol/L (2,0 mg/100 mL) including patients on renal dialysis or for patients with impaired liver function**.**

- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/100 mL), no dose adjustment is required.
- For patients with creatinine clearance is equal to or is less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher

than 0,17 mmol/L (2,0 mg/100 mL) the maximum daily dose should be one Ciprofloxacin 500 tablet. The use of Ciprofloxacin tablets is not recommended in this patient population.

Patients with renal impairment on haemodialysis:

- For patients with creatinine clearance less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/100 mL), the maximum daily dose should be one Ciprofloxacin tablet on dialysis days after dialysis. The use of Ciprofloxacin tablets is not recommended in this patient population.

Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD): - The maximum daily dose should be one 500 tablet.

Patients with hepatic impairment:

- In patients with impaired hepatic function, no dose adjustment is required.

Patients with renal and hepatic impairment:

- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/100 mL), no dose adjustment is required.
- For patients with creatinine clearance less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/100 mL) the maximum daily dose should be one C tablet.

Paediatric population

is contraindicated in children less than 18 years of age.
Safety and effectiveness of Ciprofloxacin in paediatric patients and adolescents less than 18 years of age have not been established (see sections 4.3 and 4.4).

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. Ciprofloxacin 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 ciprofloxacin 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 ciprofloxacin and tizanidine (see section 4.5).

4.4. Special warnings and precautions for use

The use of ciprofloxacin 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 ciprofloxacin 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

Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

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 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 dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.
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 coadministered 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 uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates.
Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis 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 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 ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.
Intra-abdominal infections
There are limited data on the efficacy of 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 the bones and joints
Ciprofloxacin 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.
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 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

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

Cardiovascular and cerebrovascular effects

Cases of Kounis syndrome have been reported in patients treated with ciprofloxacin (see section 4.8). Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Tendinitis and tendon rupture

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.

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 ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

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

Vision disorders

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

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 (see section 4.8).

Central Nervous System

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of non-convulsive status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). 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.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin 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 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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

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 medications. Therefore, caution should be taken when using fluoroquinolones, including Ciprofloxacin, in these populations**.** (See section 4.2 Elderly patients, section 4.5, section 4.8, section 4.9).

Dysglycaemia

As with all 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 diarrhoea 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, ciprofloxacin 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 ciprofloxacin has been reported (see section 4.8). 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 as described in section 4.2 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), 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 a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.
Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin 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 ciprofloxacin with methotrexate is not recommended (see section 4.5).
Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5. Interaction with other medicines and other forms of interactions

Medicines known to prolong QT interval
Ciprofloxacin should not be used in patients receiving medicines known to prolong the QT interval (e.g. Class IA and II antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see sections 4.3 and 4.4).

Chelation Complex Formation
The simultaneous administration of Ciprofloxacin and multivalent cation-containing medicines and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids and highly buffered medicines (e.g. antiretrovirals), containing magnesium, aluminium or calcium reduce 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 H_2 receptor blockers.

Food and Dairy Products
The concurrent administration of dairy products or mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice) and Ciprofloxacin should be avoided because the absorption of Ciprofloxacin is reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

Metoclopramide
Metoclopramide accelerates the absorption of Ciprofloxacin, 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 medicines results in a 20 % reduction of the C_{max} and AUC of Ciprofloxacin.

Theophylline
Concurrent administration of Ciprofloxacin with theophylline-containing medicines may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related side effects. If concomitant use of the two medicines cannot be avoided, plasma levels of theophylline should be monitored, and dosage adjustments made as appropriate (see Cytochrome P450 under section 4.4).

Tizanidine
In a clinical study in healthy subjects, there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC

increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect (see Cytochrome P450 under section 4.4). Tizanidine-containing medicines must not be administered together with Ciprofloxacin (see section 4.3).

Other xanthine derivatives
Concurrent administration of Ciprofloxacin with caffeine or pentoxifylline (oxpentifylline) containing products, may lead to raised serum concentrations of these xanthine derivatives.

Phenytoin
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving Ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related side effects when Ciprofloxacin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after coadministration of Ciprofloxacin with phenytoin.

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of Ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate-associated toxic reactions. Therefore, patients on methotrexate therapy should be carefully monitored when concomitant Ciprofloxacin therapy is indicated.

NSAID
Concomitant administration of the nonsteroidal anti-inflammatory drugs with quinolones such as Ciprofloxacin increases the risk of central nervous system stimulation and seizures.

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

Vitamin K antagonists
Simultaneous administration of Ciprofloxacin with warfarin may augment its anticoagulant effects. The INR should be monitored frequently during and shortly after co-administration of Ciprofloxacin with warfarin.

Oral antidiabetic agents
Concurrent administration of Ciprofloxacin and glibenclamide-containing medicines can intensify the action of glibenclamide (hypoglycaemia).

Hypoglycaemia has been reported when Ciprofloxacin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepiride), were co-administered (see section 4.8).

Duloxetine
An increase of duloxetine blood concentrations can be expected upon concomitant administration with Ciprofloxacin (see Cytochrome P450 ~~in~~ under section 4.4)

Ropinirole
Concomitant use of ropinirole with ciprofloxacin, as contained in Ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in an increase of C_{max} and AUC of ropinirole by 60 % and 84 %, respectively. Monitoring ropinirole-related side effects, dose adjustments as appropriate is recommended during and shortly after co-administration with Ciprofloxacin (see section 4.4).

Lidocaine (Lignocaine)
Concomitant use of lidocaine (lignocaine)-containing medicines with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces the clearance of intravenous lidocaine by 22 % and may increase the risk for lidocaine side effects.

Clozapine
Following concomitant administration of 250 mg ciprofloxacin 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 Ciprofloxacin are advised (see section 4.4).

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 is advised when prescribing Ciprofloxacin concomitantly with sildenafil.

ACE inhibitors and angiotensin-receptor blockers
Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury in patients with moderate to severe renal impairment and the elderly (see section 4.3).

4.6. Pregnancy and lactation

Safety of Ciprofloxacin during pregnancy and lactation has not been established.

Pregnancy
The safety of Ciprofloxacin in pregnant women has not been established. Ciprofloxacin must not be prescribed to pregnant women. Animal studies demonstrated that ciprofloxacin may damage the articular cartilage in the foetus.

Breastfeeding
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, mothers on Ciprofloxacin should not breastfeed their infants.

4.7. Effects on ability to drive and use machines

Ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to musculoskeletal and/or CNS reactions (see section 4.8).

4.8. Undesirable effects

Tabulated list of adverse reactions
The frequencies of side effects reported with ciprofloxacin in all clinical studies are summarised in the table below.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Very common (≥1/10); 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).

System Organ Class	Common	Uncommon	Rare	Very Rare

System Organ Class	Common	Uncommon	Rare	Very Rare
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis/ pseudomembranous colitis (with possible fatal outcome)	
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Life-threatening pancytopenia Life-threatening bone marrow depression
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Life-threatening anaphylactic shock Serum sickness-like reaction
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia, particularly in diabetic patients	
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in selfinjurious behaviour, such as suicidal ideations/ thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in selfinjurious behaviour, such as suicidal ideations/ thoughts and attempted or completed suicide)

Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperaesthesia Intracranial hypertension (pseudotumuor cerebri)
Eye Disorders			Visual disturbances	Visual colour distortions
Ear and Labyrinth Disorders			Tinnitus Hearing loss	Impaired hearing
Cardiac Disorders			Tachycardia	
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis
System Organ Class	**Common**	**Uncommon**	**Rare**	**Very Rare**
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthma)	
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Non infective hepatitis	Liver necrosis (which may progress to lifethreatening hepatic failure)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome

				Toxic epidermal necrolysis
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions		Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level (increased INR) Increased amylase	

The following side effects have been reported from post marketing surveillance and frequency could not be estimated.
Metabolism and Nutrition Disorders: Hyperglycaemia, hypoglycaemic coma
Nervous System Disorders: Peripheral neuropathy and polyneuropathy and Guillain-Barre syndrome **Cardiac Disorders:** QT prolongation, ventricular dysrhythmia, Torsades de Pointes *, aortic aneurysm and dissection
Skin and subcutaneous tissue disorders: Acute generalised exanthematous pustulosis (AGEP) **Investigations:** Increased International normalised ratio (INR) (in patients treated with Vitamin K antagonists)
*These events were reported during the post-marketing period (see section 4.4).

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

In clinical studies the following side effects had a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common: Vomiting, transient increase in transaminases, rash

Uncommon: Thrombocytopenia, thrombocytaemia, confusion and disorientation, hallucinations, paraesthesia and dysaesthesia, seizures, vertigo, visual disturbances, hearing loss, tachycardia, vasodilation, hypotension, transient hepatic impairment, jaundice, renal failure, oedema

Rare: Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing impaired, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to national regulatory authority.

4.9. Overdose

In overdose, side effects may be exaggerated or exacerbated (see section 4.8). In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported. Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidity, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may reduce the absorption of ciprofloxacin in overdoses. Only a small quantity of ciprofloxacin (< 10 %) is eliminated by haemodialysis or peritoneal dialysis. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones
ATC Code: J01MA02

Ciprofloxacin is a synthetic, 4-quinolone derivative with *in vitro* bactericidal activity against Gram-negative and Gram-positive organisms. Ciprofloxacin has a bactericidal action, not only in the proliferation phase but also in the resting phase. During the proliferation phase of a bacterium a segmental twisting and untwisting of the chromosomes take place. An enzyme called DNA gyrase plays a decisive part in this process. Ciprofloxacin inhibits this DNA gyrase in a way that arrests the bacterial metabolism, since vital information can no longer be read from the bacterial chromosome.
Resistance to ciprofloxacin develops slowly and in stages (multiple-step type).
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 that occurs with β-lactam antibiotics, aminoglycosides, and tetracyclines has not been observed with ciprofloxacin. Plasmid-carrying bacteria are also completely sensitive to ciprofloxacin. Parallel resistance to other important but chemically different, active substance groups, such as β-lactam antibiotics, aminoglycosides, tetracyclines, macrolide or peptide antibiotics, sulphonamides, trimethoprim or nitrofuran derivatives is not seen with ciprofloxacin.
The following microorganisms are considered inherently resistant to ciprofloxacin: *Staphylococcus aureus* (methicillin-resistant) and *Stenotrophomonas maltophilia, Actinomyces, Enteroccus faecium, Listeria monocytogenes, Mycoplasma genitalium*, *Ureaplasma urealitycum*, anaerobic microorganisms
(Except *Mobiluncus, Peptostreptococus, Propionibacterium acnes)*
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible for ciprofloxacin or not.

5.2. Pharmacokinetic properties

Ciprofloxacin modified release tablets are formulated to release the active medicinal product at a slower rate compared to immediate-release tablets. Approximately 35 % of the dose is contained within an immediate-release component, while the remaining 65 % is contained in a slow-release matrix. Ciprofloxacin tablets are designed to release all of the dose prior to the tablet reaching the distal region of the small intestine. Following oral administration of Ciprofloxacin tablets, ciprofloxacin is almost completely absorbed.
The pharmacokinetics of ciprofloxacin modified release tablets are not altered by the co-administration with food. The elimination kinetics of ciprofloxacin are similar for the immediate-release and the ciprofloxacin

modified release tablet. In studies comparing the 500 mg modified release regimen and the 250 mg bd regimen, approximately 35 % of an orally administered dose was excreted in the urine as unchanged drug for both formulations.
The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL /minute. Thus, active tubular secretion would seem to play a significant role in its elimination.
Although bile concentrations of ciprofloxacin are several folds higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 % to 2 % of the dose is recovered from the bile in the form of metabolites. Approximately 20 % to 35 % of an oral dose of immediate-release ciprofloxacin is recovered from the faeces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Crospovidone
Hypromellose 15cP
Magnesium stearate
Polyethylene glycol
Silica colloidal anhydrous
Succinic acid
Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 25 °C.
Store in a dry place.

6.5. Nature and contents of container

- Carton containing a white opaque HDPE plastic bottles with a PP child-resistant screw-cap closure with PE seal; or
- Carton containing PA/Alu/PP/aluminium foil blisters; or
- Carton containing PP/aluminium foil blisters.

6.6. Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Reyoung Pharmaceutical Co. Ltd
No. 6, Erlangshan Road, Yiyuan County, Shandong Province, China

8. REGISTRATION NUMBER

H2022/CTD8696/17137

9. DATE OF FIRST AUTHORISATION

14/02/2022

10. DATE OF REVISION OF THE TEXT

14/02/2022