Cipronat® 200 - Ciprofloxacin 2 mg/ml - *Solution for Infusion*

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is Ciprofloxacin (as Ciprofloxacin lactate).
1 ml solution for infusion contains 2 mg of Ciprofloxacin (as lactate).

2. PHARMACEUTICAL FORM

Cipronat® 200 Solution for Infusion is supplied in a transparent Type I glass vial with rubber stopper and aluminium cap. The product is a clear, yellowish to slightly yellow, odourless solution free from foreign bodies and with a pH of 3.9 to 4.5.

3. CLINICAL PROPERTIES

3.1 Therapeutic indications

Ciprofloxacin is one of a group of antibiotics called quinolones, which work by killing bacteria that cause infections. Some of the adult infections this medicine can be used against are:

- Severe systemic infection
- Lower respiratory infections
- Nosocomial pneumonia
- Ear, nose and throat infections such as acute sinusitis.
- Urinary tract infections.
- Skin and soft tissue infections
- Bone and joint infections
- Eye infections such as conjunctivitis.
- Complicated intra-abdominal infections
- Chronic bacterial prostatitis
- Pelvic infections
- Inhalation anthrax

The medicine can be taken by children and adolescents (5-17 years) with cystic fibrosis who suffer from pulmonary exacerbation associated with *P.aeruginosa* infection.
Ciprofloxacin may also be used to reduce the incidence of progression of disease or where exposure to aerosolized anthrax is suspected.
Children below the age of 5 should not be treated with Ciprofloxacin 2 mg/ml Solution for Infusion.

3.2 Posology and method of administration

Cipronat® 200 is given intravenously (into a vein) and administered by your doctor or nurse.
The usual dose for adults is 200-400 mg, twice daily. The dose used will be decided by your doctor, who will adjust it according to the type, severity and site of infection and your general state of health (e.g. kidney problems).
Your doctor or nurse will ensure that you are given this medicine as prescribed. Your doctor will tell you how long your treatment will last.
For treating a pulmonary exacerbation in patients aged 5-17 with cystic fibrosis, where the benefit is considered to outweigh the risks, the dose is 10 mg/kg IV every 8 hours (the maximum daily dose is 1200 mg). The infusion should be administered over 60 minutes.
For treating anthrax in children, a dose of 10mg/kg IV twice daily is recommended (the maximum daily dose is 800mg).
This product may also be used in adolescents and children for the treatment of other infections if the doctor considers it essential. For paediatric patients with moderate to severe infections, a dose of 6 -10 mg/kg IV every 8 hours is recommended, with the possibility of switching to oral therapy (10–20 mg/kg every 12 hours) at the discretion of the physician. The exact dosage depends on the severity of the infection.
The usual duration of treatment is between seven and fourteen days, but it may be longer if your infection is more persistent or severe. It is important that you are given a complete course of the treatment even if you begin to feel better after a few days, or your symptoms may return.

If you miss a dose of Cipronat® 200 Solution for Infusion

If you think that you may have missed a dose, talk to your doctor, nurse or pharmacist.

If you stop using Cipronat® 200 Solution for Infusion

Your doctor may decide to stop intravenous treatment and ask you to continue the treatment with Ciprofloxacin Tablets.
If you still feel unwell at the end of your prescribed course of treatment, tell your doctor. If you have any further questions on the use of this product, ask your doctor.
Cipronat® 200 Solution for Infusion is contra-indicated for children below 5 years.

Additional information: This medicinal product contains 354 mg (15.4 mmol) sodium per 100 millilitre of solution. This should be taken into account for patients on a controlled sodium diet.

3.3 Contraindications

Ciprofloxacin is contra-indicated in persons with a history of hypersensitivity to Ciprofloxacin, any member of the quinolone class of antibiotics or any of the product components. Concomitant administration with tizanidine is contra-indicated.

3.4 Special warnings and precautions for use

Before taking this medication

Do not receive Cipronat® 200 Solution for Infusion

- If you are allergic (hypersensitive) to Ciprofloxacin, to quinolone antibiotics, or to any excipient of this product. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving quinolone therapy, sometimes following the first dose. The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures should be begun.
- If the patient is under 5 years old.
- If the patient is 5-17 years old, Ciprofloxacin should not be given except for the treatment of a pulmonary exacerbation of infection in cystic fibrosis, of inhalation anthrax or unless considered essential by a doctor.
- If the patient is a pregnant woman or nursing mother.
- If the patient has a history of tendon disorders related to fluoroquinolone administration.
- Serious and fatal reactions have been reported in patients receiving concurrent administration of intravenous Ciprofloxacin and theophylline.

Special warnings

Take special care with Cipronat® 200 Solution for Infusion

- This medicine may cause a problem with your kidneys called “crystalluria”, which results in microscopic crystals forming in the urine. Providing you do not have a problem with your heart or kidneys, drinking or ensuring you receive plenty of liquid whilst being treated with Ciprofloxacin can help prevent this. However, if you experience a new pain or discomfort when passing urine whilst you are being treated with this medicine, tell your doctor.
- This medicine may occasionally cause pain and inflammation around your tendons, particularly if you are elderly or taking one of a group of medicines called steroids such as hydrocortisone. If you experience these symptoms, tell a doctor immediately and rest the affected limb.
- If you have a family history of - or know that you have - the hereditary condition called G6PD deficiency. This condition causes a deficiency of certain chemicals in the red blood cells and, if this medicine is given, it may lead to the breakdown of red blood cells, resulting in anaemia and yellowing of the skin (jaundice).
- If you develop severe and persistent diarrhoea, which may contain blood and mucus, during the course of your treatment or after stopping treatment, you should consult your doctor immediately as you may be suffering from the condition pseudomembranous colitis, which can sometimes be life threatening.
- This medicine may make your skin become more sensitive to sunlight or UV light. You should avoid exposure to strong sunlight and should not use a sun-bed or other means of UV exposure.
- If you have previously had “fits” or suffer from epilepsy or if you have ever suffered other conditions related to the central nervous system. You may feel depressed, anxious or confused whilst taking your medicine. If any of this progress to actually physically harming or wanting to physically harm yourself you should stop taking your medicine immediately and consult your doctor.
- If you have had previous problems with your liver. Your doctor may wish to check for any changes in liver function. Also, consult your doctor if you have yellowing of the whites of the eyes or skin.
- If you have a problem with your kidneys. Your doctor may wish to change your dose to allow for any reduced kidney function.

3.5 Interactions with other medicinal products

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Certain medicines are known to affect the action of Ciprofloxacin:

- Drugs that thin the blood (anticoagulants) such as warfarin or any medicines used to relieve pain and inflammation (non-steroidal anti-inflammatory drugs) such as fenbufen, but not aspirin.

- Glyburide (Glibenclamide), as severe hypoglycemia may occur if given together with Ciprofloxacin. Fatalities have been reported.
- Cyclosporin. Your doctor may want to take regular blood samples to monitor the level of a substance called creatinine in your blood.
- Phenytoin for epilepsy, as the levels of this medicine may be altered (increased or decreased) if used at the same time as Ciprofloxacin.
- Methotrexate, diazepam, duloxetine, foscarnet, methadone and zolmitriptan. Your doctor may want to do additional blood tests. Ciprofloxacin may increase plasma levels of these medicines and may worsen their side effects.
- Theophylline, as your doctor should monitor the level of theophylline in your blood. This is particularly important if you suffer from “fits” or convulsions. High levels of theophylline in the blood may be life threatening.
- Probenecid (for gout) interferes with the renal tubular secretion of Ciprofloxacin and produces an increase in its serum level.
- Tizanidine, as the serum levels of this medicine may be increased and cause an increased hypotensive and sedative effect.
- Azlocillin administered intravenously increases plasma Ciprofloxacin levels.
- Caffeine, as a reduced clearance and prolongation of serum half-life of caffeine may occur if given together with Ciprofloxacin.

The following information is intended for medical or healthcare professionals only:
This medicinal product must not be mixed with other medicinal products except for Ringer’s solution, 9 mg/ml (0.9%), sodium chloride solution, 50 mg/ml (5%) and 100 mg/ml (10%) glucose solutions, 100 mg/ml (10%) glucose/9 mg/ml (0.9%) sodium chloride and 100 mg/ml (10%) fructose solution. Active substances or solutions for reconstitution, which are chemically and physically unstable at pH 3.9-4.5, (e.g. penicillins and heparin solutions), should not be administered simultaneously.
Chemical and physical in-use stability has been demonstrated for 4 hours at 25oC. From the microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user.
The (reconstituted) solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear and colourless or slightly coloured solution should be used. If the product is inadvertently refrigerated, crystals may form. Do not use **Cipronat® 200** Solution for Infusion if you notice crystals. These crystals will, however, dissolve at room temperature and do not adversely affect the quality of this product. Only clear and colourless or slightly coloured solution should be used. Vials of any unused solution should be disposed of in accordance with local requirements.

Using Cipronat® 200 Solution for Infusion with food and drink
Ask your doctor for advice before taking any medicine. Inform your doctor before you receive Ciprofloxacin and follow their instructions.

3.6 Pregnancy and lactation
The safety and effectiveness of Ciprofloxacin in pregnant and lactating women have not been established. Ask your doctor for advice before taking any medicine. Ciprofloxacin has been shown to cause joint damage in immature animals and therefore should not be used during pregnancy or lactation.

3.7 Effects on ability to drive and use other machines
Ciprofloxacin has minor or moderate influence on the ability to drive and use machines. This applies to a greater degree at the start of treatment (when the dose is increased), when switching medication and in combination with alcohol.

3.8 Undesirable effects
Like all medicines, **Cipronat® 200** Solution for Infusion can cause adverse events although not everybody gets them. If any of the adverse events becomes serious, or if you notice any adverse event not listed in this leaflet, please tell your doctor. Adverse events that may occur include:
- Diarrhoea, feeling sick (nausea) and skin rashes (common).
- An allergic reaction such as a rash, hives, itching, small red spots on the skin or a fever. Very rarely, an allergy to Ciprofloxacin can cause facial swelling, swelling of the blood vessels in the skin and severe skin reactions such as large fluid-filled blisters, sores and ulceration and shortness of breath. Ulceration can also occur in the mouth and throat, around the anus and genital region and on the surface of the eyes. These symptoms are often accompanied by sickness, headache and fever. If you

experience any of these symptoms, treatment should be stopped and you should receive medical attention immediately (rare).
- The skin of some people may become more sensitive to the sun (rare).
- Thrush, a general feeling of being unwell or feel unsteady when walking (uncommon).
- Ciprofloxacin may make you hyperglycaemic, which means that you have high levels of the sugar glucose in your blood. If you feel unwell, have an increased need to pass water or drink more than usual, consult your doctor who can test for this condition (rare).
- Rarely, you may experience pain, pain in your fingers and/or toes, chest pain or back pain (rare).
- Rarely, you may experience inflammation in the blood vessels of the skin (rare).
- Headache, dizziness, restlessness, and either an increased or a decreased sensitivity to touch (uncommon).
- If you experience “fits” (convulsions), trembling, a tingling sensation, hallucinations, very severe headaches with visual disturbances, increased sleepiness, sleep disorders or feel anxious, confused or depressed which may progress to you actually physically harming or wanting to physically harm yourself, or you feel unsteady when walking, tell a nurse or doctor as soon as possible (very rare).
- Vomiting, indigestion, stomach ache, wind, difficulty in swallowing, loss of appetite. Rarely, a disorder called pseudomembranous colitis can occur that causes diarrhoea that may contain blood and mucus. Tell your doctor immediately if this occurs (common).
- A fast heartbeat (uncommon), fainting, hot flushes (rare), lowered blood pressure (rare), sweating, swelling of the face or limbs whilst receiving Ciprofloxacin IV.
- Bruising, jaundice, a persistent sore throat, fever with tiredness or a general feeling of being unwell, which may be due to anaemia, as Ciprofloxacin may affect certain components of the blood. In some cases, this may be life threatening (uncommon).
- Joint or tendon swelling with pain (uncommon) which may lead to tendon rupture (very rare) especially of the large tendon at the back of the ankle. If you experience these symptoms, seek medical advice immediately and rest the affected limb.
- Muscle pain, increased muscle tone, weakness or twitching (rare).
- If you suffer from the medical condition myasthenia gravis (a rare disorder of the nervous system), taking Ciprofloxacin may rarely make the symptoms of your disease become worse. If you think you are affected, tell your doctor.
- Effects on the liver such as inflammation (hepatitis) and jaundice (rare), which may rarely progress to life-threatening hepatic failure (very rare). It may cause inflammation of the pancreas, which may lead to severe pain in the upper abdomen or back (rare). It may also cause effects on the kidney that lead to pain and discomfort when passing water (crystalluria) or blood in the urine (rare). If you notice yellowing of your skin or any change in your urine output or appearance, possibly accompanied by kidney pain or pain in your abdomen or back, tell a nurse or doctor immediately.
- Rarely, people have experienced visual disturbances including blurred or double vision and colour vision disturbances, ringing in the ears and, sometimes, impaired hearing that returns to normal once treatment with Ciprofloxacin finishes (rare).
- Impaired sense of taste and smell has also been reported, these usually return to normal once treatment with Ciprofloxacin finishes (uncommon).
- Reddening of the skin, irritation or pain at the site of infusion. In some patients, inflammation of the blood vessels (very rare) of the skin may occur.

If any of side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your nurse.

3.9 Overdosage

If you think that you may have been given too much of this medicine, talk to your doctor, nurse or pharmacist.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Pharmacotherapeutic class: Antibiotic. Ciprofloxacin is a synthetic fluoroquinolone antibiotic with bactericidal action. It exhibits antibacterial activity against a wide range of gram-positive and gram-negative pathogens. When combined with other antibiotics, it shows additive and - with beta-lactam antibiotics, in particular - synergistic effects.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections:

- Aerobic gram-positive microorganisms: *Enterococcus faecalis* (many strains are only moderately susceptible), *Staphylococcus aureus* (meticillin-susceptible strains only), *Staphylococcus epidermidis* (meticillin-susceptible strains only), *Staphylococcus saprophyticus, Streptococcus pneumoniae (penicillin-susceptible strains), Streptococcus pyogenes*.
- Aerobic gram-negative microorganisms: *Citrobacter diversus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas aeruginosa, Serratia marcescens*.

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both in vitro and by use of serum levels as a surrogate marker.

The following *in vitro* data is available, but its clinical significance is unknown: Ciprofloxacin exhibits *in vitro* a minimum inhibitory concentration (MIC) of 1 µg/ml or less against most strains (>90%) of the microorganisms mentioned in the list below. However, no adequate evidence from controlled clinical trials is available:

- Aerobic gram-positive microorganisms: *Staphylococcus haemolyticus, Staphylococcus hominis, Streptococcus pneumonia* (penicillin-resistant strains).
- Aerobic gram-negative microorganisms: *Acinetobacter iwoffi, Aeromonas hydrophila, Campylobacter jejuni, Edwardsiella tardia, Enterobacter aerogenes, Klebsiella oxytoca, Legionella pneumophila, Neisseria gonorrhoeae, Pasteurella multocida, Salmonella enteritidis, Salmonella typhi, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Vibrio cholerae, Vibrio parahaemolyticus, Vibrio vulnificus, Yersinia enterocolitica.*

Most strains of *Burkholderia cepacia*, some strains of *Stenotrophomonas maltophilia*, and most anaerobic bacteria (including *Bacteroides fragilis* and *Clostridium difficile*) are resistant to Ciprofloxacin.

MECHANISM OF ACTION: It acts by inhibiting the topoisomerase II (DNA gyrase) and topoisomerase IV enzymes of bacteria. These enzymes are necessary for bacterial DNA replication, transcription, repair and recombination. Ciprofloxacin acts during both the stationary and logarithmic phases of bacterial multiplication.

4.2 Pharmacokinetic properties

A 60-minute intravenous (IV) infusion of 200 mg and 400 mg Ciprofloxacin in normal volunteers gave mean maximum serum concentrations of, respectively, 2.1 and 4.6 µg/ml and 12 hour concentrations of 0.1 and 0.2 µg/ml.

The pharmacokinetics of Ciprofloxacin are linear over an intravenous dose range of 200 to 400 mg. When pharmacokinetic parameters are compared after the first and fifth IV dose on a q 12 h regimen, no indication of drug accumulation is found. The absolute bioavailability of oral Ciprofloxacin falls within the 70-80%range, with no substantial loss by first-pass metabolism. An IV infusion of 400 mg Ciprofloxacin given over 60 minutes every 12 hours gives an area under the curve (AUC) equivalent to that produced by 500 mg given orally every 12 hours. An IV infusion of 400 mg Ciprofloxacin given over 60 minutes every 8 hours gives an AUC at steady state equivalent to that of a 750 mg oral dose given every 12 hours. A 400 mg IV dose gives a Cmax similar to that of a 750 mg oral dose. A dose of 200 mg IV every 12 hours gives an AUC equal to that of a 250 mg oral dose given every 12 hours.

After IV administration, Ciprofloxacin is found in saliva, nasal and bronchial secretions, sputum, lymph, skin blister fluid, peritoneal fluid, bile, and prostate secretions. It has also been detected in fat, muscle, skin, cartilage, bone and in the lungs. It diffuses into the cerebrospinal fluid (CSF), although CSF concentrations are usually less than 10% of peak serum concentrations.

Three metabolites of Ciprofloxacin have been identified in human urine, accounting for approximately 10% of the intravenous dose. Ciprofloxacin binds to serum protein in a range of 20 to 40% and also inhibits human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Co-administration of Ciprofloxacin with other drugs primarily metabolized by CYP1A2, such as theophylline, tizanidine and the methylxanthines, results in increased plasma concentration of these drugs and could lead to clinically significant adverseevents of the co-administered drug.

The serum elimination half-life is about 5-6 hours and the total clearance is 35 L/hr. After intravenous administration, 50-70% of the dose is excreted in the urine as unchanged drug. The renal clearance is about 22 L/hr. The urinary excretion of Ciprofloxacin is virtually complete 24 hours after dosing. About 15% of an IV dose is recovered from the faeces within 5 days of dosing.

In patients with reduced renal function, the half-life of Ciprofloxacin is slightly prolonged and dosage adjustments may be required. Preliminary studies in patients with stable chronic liver cirrhosis showed

no significant changes in the pharmacokinetics of Ciprofloxacin. There is not enough data for patients with acute hepatic insufficiency.

5. PHARMACEUTICAL PROPERTIES

5.1 List of excipients: Lactic Acid (90%), Sodium Chloride, Hydrochloric Acid 1N and water for injection.

5.2 Shelf life: Do not use **Cipronat® 200** Solution for Infusion after the expiry date given on the label. The expiry date refers to the last day of that month.

5.3 Special precautions for storage: Store in a cool and dry place below 30°C. Do not refrigerate or freeze.

Keep out of the reach and sight of children. Keep the container in the outer carton in order to protect it from light.

5.4 Legal categories: By prescription only.

6. NAME OF MANUFACTURER

Pharmathen S.A., 153 51, Pallini-Attiki, Greece.

7. REGISTRATION/LICENCE HOLDER

Dafra Pharma GmbH
Mühlenberg 7, 4052 Basel, Switzerland.

8. LAST REVISION DATE: January 2016.