



Public Assessment Report

from the Norwegian Medicines Agency

Ciprofloxacin ACS Dobfar Generics 2 mg/ml solution for infusion
ciprofloxacin

ACS Dobfar Generics SA, Luxembourg

MA-number in Norway: 05-3181

Date: 2007-06-07

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

- Module 1: Information about the initial procedure
- Module 2: Summary of product Characteristics (SPC)
- Module 3: Package Leaflet
- Module 4: Labelling
- Module 5: Scientific discussion
- Module 6: Update

Module 1: Information about the initial procedure:

1. **Type of application:** Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic application, claiming essential similarity
2. **Active substance:** ciprofloxacin
3. **Pharmaceutical form:** solution for infusion
4. **Strength:** 2 mg/ml
5. **MA holder:** ACS Dobfar Generics SA, Luxembourg
6. **Reference Member State:** Norway
7. **Concerned Member States:** Denmark, Finland and Sweden
8. **Procedure-number:** NO/H/0120/001/MR
9. **Timetable:**
Start (Day 0): 2006-09-22
End (Day 90): 2006-12-21

Module 2: Summary of product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin ACS Dobfar Generics 2 mg/ml, solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciprofloxacin lactate 2.544 mg/ml corresponding to ciprofloxacin 2 mg/ml.
Excipient: Glucose monohydrate 55 mg/ml.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the following infections in adults when caused by ciprofloxacin susceptible organisms, when oral therapy is not possible or not reliable:

- Pneumonia caused by aerobe gram-negative bacteria. Ciprofloxacin is not the active substance of choice for the treatment of pneumonia caused by *S. pneumoniae*.
- Complicated urinary tract infections
- Prostatitis
- Bacterial enteritis
- Skin and soft tissue infections caused by gram-negative bacteria
- Osteomyelitis
- Intra-abdominal infections (the anaerobic component should be covered by an appropriate antibacterial agent)
- Infections in immune-suppressed patients

Children and adolescents

Acute pulmonary exacerbation of cystic fibrosis in children and adolescents (5-17 years) caused by *Pseudomonas aeruginosa*.

Ciprofloxacin is not indicated for other infections in this age group.

Anthrax inhalation (post exposure) for adults and children: To minimize the risk of disease outburst or lessen the progress of the disease following inhalation of *Bacillus anthracis*.

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

4.2 Posology and method of administration

The dosage of intravenous ciprofloxacin is determined by the severity and type of infection, the sensitivity of the causative organism(s) and the age, weight and renal function of the patient.

The recommended dosage range for adults in different types of infection is given in the table below. The usual dosage range for adults is 200-400mg twice daily. In very serious or life threatening infections, the dosage can be increased to 400 mg three times daily.

The product may be infused directly and administered by short-term infusion over periods of 30-60 minutes. The 400mg dose should be administered over a period of 60 minutes. Initial intravenous administration may be followed by oral treatment.

The product should not be mixed with other drug products that are chemically or physically unstable at its pH of 3.9-4.5 (see section 6.2). However, Ciprofloxacin 2mg/ml Solution for Infusion has been shown to be compatible with Ringer's solution, 0.9% sodium chloride solution, 5% and 10% glucose solutions, glucose/saline and fructose 10% solution. Unless compatibility is proven, the infusion solution should always be administered separately. In addition, discard any unused portion of product immediately after use.

Adults

The following dosages for specific types of infection are recommended:

Indication	Dose intravenous (mg ciprofloxacin)
Pneumonia caused by aerobe gram-negative intravenous bacteria	200-400 mg twice daily
Complicated urinary tract infections	200-400 mg twice daily
Upper and lower urinary tract infections	200-400 mg twice daily
Upper and lower respiratory tract infection (depending on severity and sensitivity of causative organism)	200-400 mg twice daily
Cystic fibrosis patients with pseudomonal lower RTI*	400 mg twice daily
Other infections (as detailed under 4.1)	200-400 mg twice daily.

* Although the pharmacokinetics of ciprofloxacin remains unchanged in adult patients with cystic fibrosis, the low bodyweight of these patients should be taken into consideration when determining dosage.

Anthrax inhalation (post exposure)

Adults: Oral administration: 500 mg twice daily.

Intravenous administration: 400 mg i.v. twice daily.

Children: Oral administration: 15 mg/kg body weight twice daily. Maximum dose 500 mg daily, must not be exceeded (maximum daily dose 1000 mg).

Intravenous administration: 10 mg i.v./kg body weight twice daily. Maximum dose 400 mg i.v. twice daily must not be exceeded (maximum daily dose 800 mg).

Post prophylaxis exposure is only indicated if at least one of the following conditions is satisfied:

- Anthrax inhalation shown in a person that has been in the same building.
- *B. Anthracis* shown in the environmental test taken from a location or building where a person has been located and where it may have spread into the air.
- When a person has been in an area/building where it is known that the air has been contaminated with *B. Anthracis*.

Treatment must begin as soon as possible following suspicion or confirmation of exposure. When resistance determination is available however, choice of suitable treatment should be re-evaluated.

The total duration of treatment for anthrax inhalation (post exposure) with intravenous or oral ciprofloxacin is 60 days.

In impaired renal function:

Creatinine clearance ml/minute/1.73 m ²	Recommended dose adjustment
31-60 creatinine clearance (serum creatinine 120-170 µmol/liter)	Maximum daily dose i.v. 800 mg administered in 2 doses
≤ 30 creatinine clearance (serum creatinine > 175 µmol/liter)	Maximum daily dose i.v. 400 mg
≤ 30 creatinine clearance + hemodialysis (serum creatinine > 175 µmol/liter)	Maximum daily dose i.v. 400 mg. On the day of dialysis the ciprofloxacin should be administered after the dialysis
≤ 30 creatinine clearance + CAPD (serum creatinine > 175 µmol/liter)	50 mg/liter dialysis fluid 4 times per day (every 6 hours)

Monitoring of drug serum levels provides the most reliable basis for dose adjustment.

Impaired hepatic function

No adjustment of dosage is necessary.

Elderly

Although higher ciprofloxacin serum levels are found in the elderly, no adjustment of dosage is necessary.

Adolescents and children

Ciprofloxacin is not recommended for use in children below 18 years of age.

As with other medicinal products in its class, ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals.

However analysis of available safety data from ciprofloxacin used in patients below 18 years for which the majority had cystic fibrosis, did not disclose any evidence of drug related cartilage or articular damage.

Clinical and pharmacokinetic data support the use of ciprofloxacin in paediatric cystic fibrosis patients (aged 5-17 years) with acute pulmonary exacerbation associated with *P. aeruginosa* infection, at a dose of 10mg/kg intravenous three times daily (maximum daily dose 1200mg), see section 4.4 and 5.2. The infusion should be administered over 60 minutes.

Sequential therapy can also be used. Dosage as follows: 10mg/kg intravenous three times daily (maximum daily dose 1200mg) followed by 20mg/kg orally twice daily (maximum daily dose 1500mg).

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

Duration of treatment

The duration of treatment depends upon the severity of infection, clinical response and bacteriological findings. The usual treatment period for acute infections is 5-7 days.

Generally, acute and chronic infections (e.g. osteomyelitis and prostatitis, etc) where the causative organism is known to sensitive to ciprofloxacin, should be treated for at least 3 days after the signs and symptoms of the infection have disappeared.

For acute pulmonary exacerbation of cystic fibrosis associated with *P. aeruginosa* infection in paediatric patients (aged 5-17 years), the duration of treatment is 10-14 days.

4.3 Contraindications

Ciprofloxacin is contraindicated in:

- patients with a previous history of hypersensitivity to ciprofloxacin or other quinolones or to any of the excipients
- pregnancy and lactation (see section 4.6)

- patients with a history of tendon disorders related to fluoroquinolone administration (see section 4.4)
- children under 5 years

4.4 Special warnings and precautions for use

Due to the increased risk of adverse effects related to the central nervous system, the risk-benefit relationship should be carefully considered before ciprofloxacin is administered to patients with epilepsy or other disorders of the central nervous system (e.g. reduced convulsion threshold, a history of seizures, diminished cerebral blood flow, changes in brain structure or stroke).

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

Pseudomembranous colitis is a particular form of enterocolitis that can occur with antibiotics (in most cases due to *Clostridium difficile*). If severe and persistent diarrhoea occurs during or after treatment, medical advice should be sought. Even if *Clostridium difficile* is only suspected, administration of ciprofloxacin should be discontinued immediately and appropriate treatment given.

Patients with a family history of or actual defects in glucose-6-phosphate dehydrogenase activity are prone to haemolytic reactions with quinolones, and so ciprofloxacin should be used with caution in these patients.

Ciprofloxacin use has rarely been associated with photosensitivity (see section 4.8). However, patients should be recommended to avoid prolonged exposure to sunlight or UV radiation during treatment with ciprofloxacin. If this is not possible appropriate precautions should be taken.

Tendon inflammation and rupture (mainly affecting the Achilles tendon) may occur with fluoroquinolone antibiotics especially in older patients and in those treated concomitantly with corticosteroids. It is important that ciprofloxacin be discontinued at the first sign of any pain or inflammation and the affected extremity should be made non-weight bearing.

Because ciprofloxacin has some activity against *Mycobacterium tuberculosis*, false-negative cultures may occur when specimens are obtained during ciprofloxacin treatment.

Ciprofloxacin should be used with caution in patients with myasthenia gravis.

Ciprofloxacin should not be used in children and growing adolescents (5 to 17 years) except for the treatment of acute pulmonary exacerbation of cystic fibrosis, if not the benefit is considered to outweigh the potential risks. Studies in immature animals showed ciprofloxacin may cause arthropathy in weight-bearing joints. However, review of safety data in patients younger than 18 years (mainly cystic fibrosis patients) revealed no signs of medicinal product related damages to cartilage or joints.

Fluoroquinolones have been associated with prolongation of the QTc interval. Ciprofloxacin belongs to the group with a small potential to this adverse event (rate about 1 per million prescriptions). Caution should be exercised when treating patients at risk for torsade de pointes arrhythmia (see 4.8).

Ciprofloxacin ACS Dobfar Generics contain 55 mg/ml glucose monohydrate. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Ciprofloxacin inhibits CYP1A2. When given concomitantly this may give increased serum concentrations of substrates that is metabolised with this enzyme (e.g. theophylline, clozapine, tacrine, ropinirole, tizanidine). When these drugs are given concomitantly with ciprofloxacin the patient

should be monitored carefully for signs of overdose. Measuring of serum concentration may be necessary, especially for theophyllin.

Caffeine:

The metabolism of caffeine is inhibited by ciprofloxacin resulting in doubled plasma concentration.

Glibenclamide

In isolated cases concomitant use of ciprofloxacin and glibenclamide may increase the effect of glibenclamide and give hypoglycaemia.

Mexiletine

Simultaneous administration of ciprofloxacin and mexiletine can lead to increased concentrations of mexiletine

Phenytoin

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

Warfarine

Ciprofloxacin, as for other quinolones, may increase the effect of coumarin-derivatives (incl. warfarine).

When given concomitantly, the INR-value should be monitored and suitable anticoagulation tests should be performed. The dose of oral anticoagulation treatment should be adjusted if needed.

Ciclosporine

Isolated reports indicate that concomitant use of ciprofloxacin may give additive nephrotoxic effects. Studies indicate that ciprofloxacin may counteract ciclosporin's inhibitory effect on the interleukin-2-production. Retrospective studies indicate that ciprofloxacin may cause increased rejection frequency. The serum creatinine concentration must be monitored.

Probenicid

Probenicid inhibits the tubular secretion of ciprofloxacin and cause increased plasma concentration.

Contraceptives, birth control pills

Some antibiotics may, in rare cases, reduce the effect of the birth control pill by disturbing the bacterial hydrolysis of steroid conjugate in the intestine and thereby reduce the re-absorption of unconjugated steroid. However no evidence of pharmacokinetic interactions between ciprofloxacin and contraceptives has been seen in clinical studies.

Methotrexate

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

4.6 Pregnancy and lactation

Use during pregnancy is contraindicated. As with other quinolones, ciprofloxacin has been shown to cause arthropathy in immature animals, and therefore its use during pregnancy is contraindicated. Administration to breast-feeding mothers is contraindicated since quinolones administered at therapeutic doses are excreted in breast milk in quantities that can be expected to affect the infant (see section 4.3).

For the indication anthrax inhalation (post exposure) the risk/benefit evaluation summons that treatment of pregnant and breastfeeding women are appropriate. When determination of resistance

exists changing to a medication with better risk profile is however recommended. (See also section 4.2).

4.7 Effects on ability to drive and use machines

The medication is presumed to normally not influence the ability to drive and use machines.

Patients should be informed that ciprofloxacin may cause dizziness, sleepiness and headache, especially in the beginning of the treatment, which may cause reduced reaction.

4.8 Undesirable effects

Approximately 5-14% of patient can be expected to experience adverse reactions. The most commonly reported adverse reactions involve the gastro-intestinal tract and the central nervous system.

The following undesirable effects have been observed:

Very common ($\geq 1/10$)

Common ($\geq 1/100, < 1/10$)

Uncommon ($\geq 1/1,000 \leq 1/100$)

Rare ($\geq 1/10,000, \leq 1/1,000$)

Very rare ($\leq 1/10,000$)

Blood and lymphatic system disorders

Uncommon: Eosinophilia, leucopenia, granulocytopenia, anaemia, thrombocytopenia.

Very rare: Leucocytosis, thrombocytosis, haemolytic anaemia, pancytopenia, agranulocytosis, altered prothrombin values, hyperglycaemia.

A transient increase in bilirubin may also be observed.

Immune system disorders

The following reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, ciprofloxacin is to be discontinued immediately and the treating physician informed.

Common: Skin reactions such as rash, pruritus, and drug fever.

Very rare: Punctiform cutaneous bleeding (petechiae), vesicles with haemorrhage (haemorrhagic bullae) and small nodules (papules) with crust formation showing vascular involvement (vasculitis), urticaria, erythema nodosum, erythema multiforme (mild to severe forms i.e. Stevens-Johnson syndrome), Lyell syndrome. Interstitial nephritis, hepatitis, and hepatic necrosis to life-threatening hepatic failure. Anaphylactic/anaphylactoid reactions (e.g. ranging from facial, vascular and laryngeal oedema, through dyspnoea to shock), in some cases with the first dose of the medicinal product. If such reactions occur, ciprofloxacin is to be discontinued immediately, and medical treatment for shock should be given.

Nervous system disorders

Common: Dizziness, headache, tiredness, agitation, tremor, confusion.

Very rare: Insomnia, paraesthesiae, sweating, ataxia, convulsive seizures (the spasmodic threshold in epilepsy may be reduced), increased intracranial pressure, migraine, anxiety states, nightmares, distress, depression, hallucinations, aggravation of myasthenia, psychotic reactions (involving in some cases a risk of self-injury), asthenia.

These reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, ciprofloxacin is to be discontinued immediately and the treating physician informed.

Eye disorders

Very rare: Disturbed vision (e.g. diplopia, chromatopsia).

Ear and labyrinth disorders

Very rare: Tinnitus, transient (especially high-frequency) hearing loss.

Cardiac disorders

Uncommon: Palpitation.

Very rare: Tachycardia. Torsade de pointes, QT prolongation. These events were observed predominantly among patients with further risk factors for QTc prolongation (see section 4.4).

Vascular disorders

Very rare: Peripheral oedema, hot flushes, fainting,

Respiratory, thoracic and mediastinal disorders

Uncommon: Pulmonary embolism, dyspnoea, pulmonary oedema, haemoptysis.

Gastrointestinal disorders

Common: Nausea, diarrhoea, vomiting, digestive disorders, abdominal pain, flatulence, loss of appetite.

Uncommon: Hiccough.

Rare: Pseudomembranous colitis.

Hepato-biliary disorders

Patients with liver damage in particular may show a transient rise in transaminases and alkaline phosphatase or even cholestatic jaundice.

Skin and subcutaneous tissue disorders

Very rare: Photosensitivity (see section 4.4).

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia and joint swelling.

Very rare: Muscular pains, inflammation of tendon sheaths (tenosynovitis); tendonitis and torn tendons (e.g. of Achilles' tendon) may occur during treatment with fluoroquinolones. These events were observed predominantly among older patients who had been systemically treated beforehand with corticosteroids.

Renal and urinary disorders

Very rare: Crystalluria, haematuria, transient impairment of kidney function to transient renal failure, interstitial nephritis.

General disorders and administration site conditions

Uncommon: Epitaxis.

Very rare: Dysgeusia and dysosmia as well as a possible loss of the sense of smell, which normally recovers after the end of the therapy.

Local reactions on the site of injection for intravenous administration of ciprofloxacin have been reported. These reactions are more frequent if infusion time is 30 minutes or less. It may appear as local skin reactions that disappear rapidly after completion of infusion. Following intravenous administration is not contraindicated if the reaction does not return or aggravate.

Long-term and repeated use of ciprofloxacin can lead to super-infections with resistant bacteria or fungi.

4.9 Overdose

In cases of acute, high overdosing it has, in some cases, been reported reversible kidney toxicity. It is therefore recommended, beyond normal emergency measures, to measure the kidney function. Only small amounts ciprofloxacin (<10%) can be removed using haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimicrobial products for systemic use, fluoroquinolones.

ATC code: J01M A02

Mode of action: Ciprofloxacin is a gyrase-inhibitor with bactericide effect. In the reproduction phase chromosomes in the bacteria are turned and twisted in segments. The enzyme DNA- gyrase plays an important role in this process. Ciprofloxacin inhibits the DNA-gyrase so that the bacterial metabolism stops because vital information no longer can be read from the bacterial chromosome.

Mechanism(s) of resistance

Cross-resistance between fluoroquinolones may occur when the mechanism of resistance is due to mutations in bacterial gyrases. However, single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all active substances within the class. Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physicochemical properties of the various active substances within the class and the affinity of transport systems for each active substance.

Breakpoints

EUCAST clinical MIC (from 30 April 2004):

Organism	Susceptible	Resistant
<i>Enterobacteriaceae</i>	≤0.5 mg/ml	>1.0 mg/ml
<i>Pseudomonas</i> spp.	≤0.5 mg/ml	>1.0 mg/ml
<i>Acinetobacter</i> spp.	≤1.0 mg/ml	>1.0 mg/ml
<i>Staphylococcus</i> spp. ¹	≤1.0 mg/ml	>1.0 mg/ml
<i>Streptococcus pneumoniae</i> ²	≤0.25 mg/ml	>2.0 mg/ml
<i>H. influenzae</i> and <i>M.catarrhalis</i> ³	≤0.5 mg/ml	>0.5 mg/ml
Non-species related breakpoints ⁴	≤0.5 mg/ml	>1.0 mg/ml

¹*Staphylococcus* spp – breakpoints relate to high dose therapy

²*Streptococcus pneumoniae* – wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin and is therefore categorized as intermediate.

³*Haemophilus/Moraxella* – ciprofloxacin low-level resistance (MIC:s of 0.125-0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae*.

⁴Non-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.

Susceptibility

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.

Commonly susceptible species
Gram-positive aerobes
<i>Bacillus anthracis</i>

Gram-negative aerobes
<i>Citrobacter</i> spp.
<i>Haemophilus influenzae</i>
<i>Moraxella</i> spp.
<i>Moraxella catarrhalis</i>
<i>Morganella</i> spp.
<i>Proteus</i> spp.
<i>Proteus vulgaris</i>
<i>Salmonella</i> spp.
<i>Serratia</i> spp.
<i>Shigella</i> spp.
<i>Vibrio</i> spp.
<i>Yersinia enterocolitica</i>
Other pathogens
<i>Legionella pneumophila</i>
Species for which acquired resistance may be a problem
Gram-positive aerobes
<i>Enterococcus faecalis</i>
<i>Staphylococcus aureus</i> (methicillin resistant, MRSA) ⁺
<i>Staphylococcus aureus</i> (methicillin susceptible)
<i>Streptococcus agalactiae</i>
<i>Streptococcus pneumoniae</i>
<i>Streptococcus pyogenes</i>
Gram-negative aerobes
<i>Acinetobacter</i> spp.
<i>Burkholderia cepacia</i>
<i>Campylobacter</i> spp.
<i>Citrobacter freundii</i>
<i>Enterobacter</i> spp.
<i>Enterobacter cloacae</i>
<i>Escherichia coli</i>
<i>E. coli</i> ESBL producing ⁺
<i>Klebsiella oxytoca</i>
<i>Klebsiella pneumoniae</i>
<i>Klebsiella pneumoniae</i> ESBL producing ⁺
<i>Morganella morganii</i>
<i>Neisseria gonorrhoeae</i>
<i>Proteus mirabilis</i>
<i>Pseudomonas aeruginosa</i>
Other pathogens
<i>Chlamydia</i> spp.
<i>Mycoplasma pneumoniae</i>
Inherently resistant organisms
Gram-positive aerobes
<i>Enterococcus</i> spp.
<i>Enterococcus faecium</i>
Gram-negative aerobes
<i>Stenotrophomonas maltophilia</i>
Other pathogens
<i>Treponema pallidum</i>

<i>Ureaplasma urealyticum</i>
Anaerobes
<i>Bacteroides fragilis</i>
<i>Clostridium difficile</i>

+ resistance rate > 50 % in one or more countries

MRSA are very likely to be resistant to ciprofloxacin and ciprofloxacin should not be used to treat presumed or known MRSA infections unless the organism is known to be susceptible.

Abbreviations: ESBL: Extended Spectrum Beta-lactamases.

Anthrax inhalation (post exposure) – additional information

Obtained serum concentrations of ciprofloxacin in humans are used as a surrogate endpoint, that most likely is considered to predict the clinical use and is the basis for the indication anthrax inhalation (post exposure).

The average serum concentrations of ciprofloxacin associated with a statistical significant improvement of survival of anthrax inhalation in rhesus monkeys is attained or surpassed in adult patients and children receiving oral or intravenous treatment with ciprofloxacin (See section 4.2). Ciprofloxacin's pharmacokinetics has been examined in various populations of humans. Average maximum concentration attained in the serum at steady state in adults that were administered 500 mg orally every 12 hours is 2.97 µg/ml and 4.56 µg/ml following 400 mg administered intravenously every 12 hours. The average lowest concentration in the serum at steady state for both these regimes is 0.2 µg/ml.

In a study with 10 pediatric patients between 6 and 16 years of age, given intravenous infusions every 30 minutes with ciprofloxacin 10 mg/kg body weight with 12 hours intervals, a peak concentration in the serum of 8.3 µg/ml was attained while the lowest concentration was between 0.09 and 0.26 µg/ml. The patients that following the second intravenous infusion was changed to oral treatment with 15 mg/kg bodyweight every 12 hours attained an average peak concentration of 3.6 µg/ml after the initial oral dose.

Safety data for long term treatment with ciprofloxacin in children, including the effect on the cartilage, is limited (see also section 4.4).

A placebo controlled animal study was conducted on rhesus monkeys that were exposed to an average inhaled dose of *B. Anthracis* of 8 LD₅₀ (~5,5 x 10⁵) spores (range 5-30 LD₅₀). The least inhibited concentration (MIC) for ciprofloxacin for the stem of anthrax that was used was 0.08 µg/ml. In the investigated animals the average attained serum concentration of ciprofloxacin at expected T_{max} (1 hour after administration) varied from 0.98 to 1.69µg/ml, following oral administration to steady state. Average lowest concentration at steady state 12 hours after dosages varied from 0.12 to 0.19 µg/ml. Fatality due to anthrax in the animals that were treated for 30 days with ciprofloxacin orally, treatment commencing 24 hours after exposure, was significantly lower (1/9) compared with the placebo group (9/10) (p=0.001). The one ciprofloxacin treated animal that died due to anthrax, did so after completing 30 days of treatment.

5.2 Pharmacokinetic properties

Pharmacokinetics of ciprofloxacin is linear for intravenous administration of dosages up to 400 mg. Following an intravenous infusion of 200 mg ciprofloxacin administered in 30 minutes, a maximum serum concentration of 3-4 mg/l is obtained.

Half-life for serum elimination following oral and intravenous administration was similar and varied from 4 to 6 hours.

With 60 minutes infusion time a similar AUC was obtained with the following dosages:

200 mg i.v. every 12 hours	250 mg orally every 12 hours
400 mg i.v. every 12 hours	500 mg orally every 12 hours
400 mg i.v. every 12 hours*	750 mg orally every 12 hours*
400 mg i.v. every 8 hours	750 mg orally every 12 hours

*also corresponding to C_{max} .

Distribution

Ciprofloxacin has low protein binding (20 – 30%), and the substance is present in plasma mainly in a non-ionized form. Ciprofloxacin can freely diffuse into the extra cellular space. The high steady state distribution volume of 2 – 3 l/kg body weight demonstrate that ciprofloxacin is distributed in body fluids and passes into tissue and provide concentrations that most often surpass the corresponding serum level.

Metabolism

Ciprofloxacin is excreted mainly unchanged through the kidneys and in lesser degree in the faeces (15%) and bile (1%).

Ciprofloxacin is excreted almost completely within 24 hours.

Small concentrations of 4 metabolites have been found, these are less anti-bacterial active than ciprofloxacin.

Patient factors: In reduced renal function a dose-adjustment is necessary (see section. 4.2).

5.3 Preclinical safety data

Like other gyrase inhibitors, ciprofloxacin may induce joint damage during the growth phase of juvenile animals. Other preclinical effects were observed only at exposures that were sufficiently in excess of the maximum human exposure that concern for human safety is negligible.

Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of Ciprofloxacin *in vitro* and in animal experiments in comparison with other fluoroquinolones.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid
Glucose monohydrate
Water for injections

6.2 Incompatibilities

No addition to the solution for infusion is recommended.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Keep the bag in the foil in order to protect from light.

6.5 Nature and contents of container

PVC polymer bag in foil.

10 x 100 ml bag

10 x 200 ml bag

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No addition to the solution for infusion is recommended.

The bag should be stored in the overpouch until use in order to protect from light.

To be used immediately after the bag is opened. Discard any unused portion of product immediately after use.

Do not use if you notice visible signs of deterioration.

7. MARKETING AUTHORISATION HOLDER

ACS Dobfar Generics S.A.

5, Rue Eugene Ruppert

L-2453 LUXEMBURG

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

12/2006

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin ACS Dobfar Generics, 2 mg/ml, Solution for infusion Ciprofloxacin

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ciprofloxacin ACS Dobfar Generics is and what it is used for
2. Before you use Ciprofloxacin ACS Dobfar Generics.
3. How to use Ciprofloxacin ACS Dobfar Generics.
4. Possible side effects.
5. How to store Ciprofloxacin ACS Dobfar Generics.
6. Further information.

1. WHAT CIPROFLOXACIN ACS DOBFAR GENERICS IS AND WHAT IT IS USED FOR

Ciprofloxacin ACS Dobfar Generics is an antibiotic, a medicinal product that is effective against bacterial infections. Ciprofloxacin belongs to the group quinolones. This prevents normal function and formation of the bacteria.

Ciprofloxacin ACS Dobfar Generics is used in the treatment of several types of infections such as:

- Pneumonia
- urinary tract infections,
- infections in the prostate,
- infections in the abdomen and around the gut,
- certain skin infections
- infections in the bones
- Infections in patients with poor immune system.

Ciprofloxacin ACS Dobfar Generics may also be used for treating lung infections in children and teenagers (age 5–17) who have cystic fibrosis.

Ciprofloxacin ACS Dobfar Generics is also used to reduce the risk or alleviate the course of illness, following inhalation of anthrax bacteria.

2. BEFORE YOU USE CIPROFLOXACIN ACS DOBFAR GENERICS

Do not use Ciprofloxacin ACS Dobfar Generics:

- if you are allergic (hypersensitive) to ciprofloxacin or any of the other ingredients of Ciprofloxacin ACS Dobfar Generics
- if you are hypersensitive (allergic) to any other quinolones
- if you are pregnant, think you may be pregnant or you are breast-feeding
- if you have or have had problems with your tendons caused by quinolone antibiotics

Children under 5 years old must not be treated with Ciprofloxacin.

Take special care with Ciprofloxacin ACS Dobfar Generics

- if you are a growing youth unless you are using it because you have inhaled anthrax.
- if you are an epileptic or have a tendency of cramps and similar central nervous system problems the doctor will evaluate the medical value of ciprofloxacin prior to treatment.
- if you or any member of your family have a deficiency in the blood called glucose-6-phosphate dehydrogenase (G6DP)
- if you have a problem with weakness in your muscles called myasthenia gravis if tenderness or swelling occur on the back of the heel (Achilles tendons) during treatment, especially if you recently have been treated with corticosteroids. If you experience these symptoms, you must tell your doctor immediately and rest the affected limb.
- if you have reduced kidney function.
- note that exposure to strong sunlight or use of solarium during treatment is not recommended.
- if you have certain heart rhythm disturbances, torsade de pointes.
- you should make sure you get enough fluid, otherwise you may experience crystal in the urine, which can be very painful

If you develop severe and persistent diarrhoea, which may contain blood and mucus, during your treatment or after stopping treatment, you must consult your doctor immediately as you may be suffering from the condition pseudomembranous colitis, which sometimes can be life-threatening.

Ciprofloxacin can interfere with the results of laboratory tests for tuberculosis. If you need to be tested for tuberculosis while you are treated with Ciprofloxacin, it is important to inform your doctor or the nurse about your treatment.

Pregnancy and breast feeding

You must not be given Ciprofloxacin ACS Dobfar Generics if you are pregnant, think you might be pregnant or if you are breast-feeding. There is a risk that Ciprofloxacin ACS Dobfar Generics may harm the foetus or the newborn child.

Using other medicines while using Ciprofloxacin ACS Dobfar Generics:

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

Ciprofloxacin may interfere with other medicines.

Particular care should be taken if you are receiving any of the following substances:

- Anticoagulants such as warfarin (for thromboembolic disease)
- Atropine (for bradycardia, and as general anaesthetic)
- Benzodiazepines such as diazepam (used as anticonvulsant and sedative and for anxiety) and midazolam (sedative and used as general anaesthetic)
- Ciclosporin (immunosuppressive medicine)
- Clozapine (for schizophrenia)
- Glibenclamide (for diabetes type 2)
- Hyoscine (for motion sickness, as general anaesthetic and as antispasmodic)
- Medicine containing caffeine
- Mexiletine (for unstable heart function)
- Methotrexate (for cancer)

- Metoclopramide (anti-emetic medicine)
- NSAIDs such as ibuprofen (for mild to moderate pain and rheumatism)
- Papaverine (for spasm in the gastrointestinal tract)
- Pentoxifylline (for claudicatio intermittens)
- Phenytoin (for epilepsy)
- Probenecid (used to treat gout)
- Ropinirole (for Parkinson's disease)
- Tacrine (for Alzheimer's disease)
- Tizanidine (for spasticity and acute muscle spasm)
- Theophylline (for asthma)

Driving and using machines

Ciprofloxacin can cause side effects such as dizziness or confusion which may affect your ability to drive or operate machinery. This is more likely to happen at the start of treatment, when dose is increased, when switching treatment or if you drink alcohol.

Important information about some of the ingredients of Ciprofloxacin ACS Dobfar Generics

Ciprofloxacin ACS Dobfar Generics contain 55 mg/ml glucose monohydrate. This should be taken into account in patients with diabetes mellitus.

3. HOW TO USE CIPROFLOXACIN ACS DOBFAR GENERICS

This medicine will be given to you by a healthcare professional. The dose is set by the doctor and he adjusts the dose for you.

The medicine will be given as an infusion into a vein and it should be given during at least 30 – 60 min. Two or three infusions per day are normal.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin ACS Dobfar Generics can cause side effects, although not everybody gets them.

Common (happens in 1 to 10 out of 100 patients)

Skin reactions as rash, itching and drug fever, nausea, diarrhoea, vomiting, digestive disorders, abdominal pain, flatulence, loss of appetite, dizziness, headache, tiredness, restlessness, tremor and confusion.

Uncommon (happens in 1 to 10 out of 10.000 patients)

Hiccough, joint pain, joint swelling, nose bleeding, rapid heart beat, dyspnoea, pulmonary oedema, blood in the saliva, pulmonary embolism, anaemia.

Rare (happens in 1 to 10 out of 10.000 patients)

Infection in colon.

Very rare (happens in less than 1 out of 10.000 patients)

If any of the following reactions occur, even with the first dose of treatment, inform your doctor or nurse immediately, they may choose to discontinue your treatment.

Some of these side effects are very serious and you may need urgent medical attention.

Aggravation of myasthenia gravis, increased pressure in the brain, loss of control of bodily movements, convulsive seizures (the spasmodic threshold in epilepsy may be reduced), migraine, anxiety states, nightmares and hallucinations.

Skin reactions on the face, limbs and the mucosa in the mouth (mild to severe forms i.e. Steven-Johnson syndrome) and Lyell syndrome, petechia, skin bobbles with blood, blisters with crust formation, red painful lumps of the skin (erythema nodosum) and urticaria.

Infection in the kidneys, hepatitis, hepatic necrosis to life-threatening hepatic failure. Increased intracranial pressure, anaphylactic reaction e.g. ranging from facial, vascular and laryngeal oedema to dyspnoea and shock, happens in some cases with the first dose of the medicinal products and psychotic reactions (including in some cases a risk of self-injury).

Other **very rare** side effects:

Disturbed vision, tinnitus, transient hearing loss, photosensitivity, disturbance of sense of taste and smell or possible loss of the sense of smell, insomnia, abnormal touch sensation such as burning, prickling or formication, sweating, distress, depression, tachycardia, heart rhythm disturbances, swelling of the limbs, hot flushes, fainting, muscular pain, inflammation of tenosynovitis, infection of tendons and torn tendons, crystals or blood in the urine, transient impairment of kidney function to transient renal failure, hyperglycaemia.

In addition hereto changes in the level of blood corpuscles can be observed.

Patients with liver damage in particular may show a transient rise in certain liver enzymes or even jaundice; a transient increase in bilirubin may also be observed.

Long-term and repeated use of Ciprofloxacin can lead to super-infections with resistant bacteria or fungi.

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

5. HOW TO STORE CIPROFLOXACIN ACS DOBFAR GENERICS

Keep out of the reach and sight of children.

Must not be stored in the refrigerator or freezer.

Keep the infusion bag in the foil until use in order to protect from light. To be used immediately after the bag is opened. Discard any unused portion of product immediately after use.

Do not use Ciprofloxacin ACS Dobfar Generics after the expiry date stated on the bag. The expiry date refers to the last day of that month.

Do not use Ciprofloxacin ACS Dobfar Generics if you notice visible signs of deterioration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ciprofloxacin ACS Dobfar Generics contains

- The active substance is ciprofloxacin lactate equivalent to ciprofloxacin 2 mg/ml.
- The other ingredients are lactic acid, glucose monohydrate and water for injection.

What Ciprofloxacin ACS Dobfar Generics looks like and contents of the pack

Ciprofloxacin ACS Dobfar Generics is a clear solution, free from visible particles. It comes in polymer plastic bags of 100 ml or 200 ml which is wrapped in a foil.

Marketing Authorisation Holder

ACS Dobfar Generics S.A.
5, Rue Eugene Ruppert
L-2453 LUXEMBOURG

Manufacturer:

Facta Farmaceutici S.P.A.
Teramo
Italia

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

FARMAPLUS AS
Postboks 202
1372 ASKER

This leaflet was last approved in 12/2006.

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The following information is intended for medical or healthcare professionals only:

No additions should be done to the solution for infusion.

Module 4: Labelling

Not included.

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Ciprofloxacin ACS Dobfar Generics 2 mg/ml solution for infusion. The procedure was finalised at 2006-12-21 (on Day 90). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Type of marketing authorisation, main features of disease/condition etc, discussion in CMD(h)

Based on review of the submitted data, the Member States have granted a marketing authorisation (MA) for Ciprofloxacin ACS Dobfar Generics 2 mg/ml solution for infusion from ACS Dobfar Generics SA. The first date of authorisation in Norway was 22. December 2005. The product is indicated for the following infections:

“Serious salmonella infections, complicated urinary tract infections and osteomyelitis caused by gram-negative rod shaped bacteria susceptible to ciprofloxacin where treatment with oral medications is not possible.

Urosepsis and septicaemia caused by ciprofloxacin susceptible bacteria.

Serious gastroenteritis caused by Salmonella and Shigella species where antimicrobial medication is required.

Anthrax inhalation (post exposure) for adults and children: To minimize the risk of disease outburst or lessen the progress of the disease following inhalation of *Bacillus anthracis*.

Official instructions concerning the appropriate use of antimicrobial medication must be taken into account when implementing antibiotic treatment.”

A comprehensive description of the indications and posology is given in the SPC (see Module 3).

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application.

This concerns a generic application claiming essential similarity to the innovator product Ciproxin «Bayer». Ciproxin (2 mg/ml solution for infusion) has been marketed in Norway since 1993-03-11. In addition, reference is also made to Ciproxin authorisations in the individual Member States (reference product). This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain.

Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. Since this product is an aqueous solution and intended to be administered intravenously, a bioequivalence study is not necessary.

No new pre-clinical and clinical studies were conducted, which is acceptable for this generic application.

I. QUALITY ASPECTS

I.1 Introduction

Pharmaceutical form, formulation, container system, etc

Ciprofloxacin ACS Dobfar is presented in the form of a solution for infusion 2 mg/ml. The drug substance is present as ciprofloxacin lactate corresponding to 2 mg/ml ciprofloxacin. The excipients are lactic acid, glucose monohydrate and water for injections. The powder for solution for injection/infusion is packed in PVC polymer bags in foil.

I.2 2.2 Drug Substance

INN; chemical features like chemical class, chirality, manufacturing, specifications, stability

Ciprofloxacin has a monograph in the Ph.Eur. and the manufacturer holds a Certificate of Suitability of the monograph. It is an almost white or pale yellow, crystalline powder, which is practically insoluble in water.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are sufficiently described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

I.3 Medicinal Product

Pharmaceutical development, manufacture of the product, product specification, stability of the product

Ciprofloxacin solution for infusion 2 mg/ml is formulated with the excipients lactic acid, glucose monohydrate and water for injections. The product incorporates conventional excipients which are controlled by their corresponding Ph. Eur. monographs. The product development has taken the physico-chemical characteristics of the active substance into consideration.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC. The long term storage conditions are: Do not refrigerate or freeze. Keep the bag in the foil in order to protect from light.

II. NON-CLINICAL ASPECTS

Ciprofloxacin ACS Dobfar Generics has been shown to be essential similar to the approved product Ciproxin «Bayer». For this abridged application, non-clinical data have not been submitted and are not considered necessary.

III. CLINICAL ASPECTS

Ciprofloxacin is a well-known active substance with established efficacy and safety.

The generic product Ciprofloxacin ACS Dobfar Generics is an aqueous solution and intended to be administered intravenously. It contains the same concentration of the same active substance (ciprofloxacin lactate) in the same pharmaceutical form as the Norwegian originator Ciproxin «Bayer». Due to the above-mentioned reasons, Ciprofloxacin ACS Dobfar Generics can be considered essentially similar to the original product Ciproxin, and a bioequivalence study is not required. Clinical efficacy and safety issues can further be referred to the original product.

The content of the SPC for Ciprofloxacin ACS Dobfar Generics, approved during the mutual recognition procedure, is in accordance with that for the original product Ciproxin «Bayer».

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ciprofloxacin ACS Dobfar Generics 2 mg/ml solution for infusion is a generic to Ciproxin «Bayer». Ciproxin is a well-known medicinal product with an established efficacy and safety profile.

The product is an aqueous solution and intended to be administered intravenously. A bioequivalence study is therefore not necessary. The SPC is consistent with that of the original product.

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

The Member States mutually recognised the Norwegian evaluation and the marketing authorisation. There was no discussion in the CMD(h). Agreement between Member States was reached through a written procedure.

Module 6: Update

List of abbreviations

CMD (h)	Co-ordination Group for Mutual Recognition and Decentralised procedures (human)
ICH	International Conference of Harmonisation
MA	Marketing Authorisation
Ph.Eur.	European Pharmacopoeia
SPC	Summary of Product Characteristics