ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
NL	Hikma Farmacêutica (Portugal) Lda. Estrada do Rio da Mó, nº8, 8A & 8B, Fervença, 2705-906 Terrugem SNT, PORTUGAL		Ciprofloxacin Hikma 200mg/100ml Oplossing voor Intraveneuze Infusie	2mg/ml	Solution for infusion	Intravenous use	200mg/100ml
AT		Hikma Farmacêutica (Portugal) Lda. Estrada do Rio da Mó, nº8, 8A & 8B, Fervença, 2705-906 Terrugem SNT, PORTUGAL	Ciprofloxacin Hikma 200mg/100ml Infusionslösung	2mg/ml	Solution for infusion	Intravenous use	200mg/100ml
DE		Hikma Farmacêutica (Portugal) Lda. Estrada do Rio da Mó, nº8, 8A & 8B, Fervença, 2705-906 Terrugem SNT, PORTUGAL	Ciprofloxacin Hikma 200mg/100ml Lösung zur intravenösen Anwendung	2mg/ml	Solution for infusion	Intravenous use	200mg/100ml
IE		Hikma Farmacêutica (Portugal) Lda. Estrada do Rio da Mó, nº8, 8A & 8B, Fervença, 2705-906 Terrugem SNT, PORTUGAL	Ciprofloxacin Hikma 200mg/100ml Solution for Infusion	2mg/ml	Solution for infusion	Intravenous use	200mg/100ml
IT		Hikma Farmacêutica (Portugal) Lda. Estrada do Rio da Mó, nº8, 8A & 8B, Fervença, 2705-906 Terrugem SNT, PORTUGAL	Ciprofloxacin Hikma 200mg/100ml Soluzione per Infusione Endovenosa	2mg/ml	Solution for infusion	Intravenous use	200mg/100ml
UK		Hikma Farmacêutica (Portugal) Lda. Estrada do Rio da Mó, nº8, 8A & 8B, Fervença, 2705-906 Terrugem SNT, PORTUGAL	Ciprofloxacin Hikma 200mg/100ml Solution for Infusion	2mg/ml	Solution for infusion	Intravenous use	200mg/100ml

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CIPROFLOXACIN HIKMA AND ASSOCIATED NAMES (see Annex I)

Ciprofloxacin is a quinolone effective *in vitro* against a large number of Gram-negative aerobic bacteria as well as against some Gram-positive organisms.
Management of patients with complicated urinary tract infections (UTIs) currently includes empirical treatment with a broad-spectrum antibiotic (fluoroquinolone), and potential subsequent treatment for 10-14 days based on urine culture and sensitivity. In order to avoid treatment failure and emergence of resistance it is a prerequisite that patient's compliance and dosing be adequate.

The applicant/MAH did not submit any clinical data to address the CHMP questions related to the risk/benefit of the proposed dose in UTIs and the maximum adult daily dose, as this application is a so called ″generic″ application (reference product/originator Ciproxin from Bayer).

The body of published literature and resistance data presented by the applicant provided adequate justification, both from an efficacy and safety (more likely to prevent bacterial resistance and no increase in adverse reactions) viewpoint, for the dosing regimen of 200-400 mg ciprofloxacin twice daily for the treatment of complicated UTI.
This product being a solution intended for intravenous infusion, should be restricted to the treatment of complicated UTI's.
From the published data, which have demonstrated for the proposed maximum dose 400 mg intravenous three times daily as a maximum dose, a superior prevention of antibiotic resistance without a significant increase in adverse reactions in serious and life-threatening infections of other organ systems, there is no reason to conclude that this favourable risk/benefit profile would differ significantly in the treatment of complicated UTIs.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- The literature provided by the applicant support a dose of 200 – 400 mg twice daily in the treatment of complicated urinary tract infections and a maximum adult daily dose of 400 mg three times daily.

- The requested amendments to section 5.1 of the Summary of Product Characteristics including the breakpoints relevant to the indications are acceptable.

The CHMP has recommended that the indication should be complicated urinary tract infections with a recommended dose of 200 – 400 mg twice daily. In addition the maximum daily dose for the use of ciprofloxacin should be 400 mg three times daily.

In addition, other amendments to the Summary of Product Characteristics, labelling and package leaflet not in relation with the outcome of the referral procedure were included in accordance with the Guideline on SPC, excipient guideline and the latest Quality Review of Documents templates.

The CHMP has therefore recommended the granting of the Marketing Authorisation(s) and the amendment of the Summary of Product Characteristics, labelling and package leaflet of the Reference Member State. These are set out in Annex III for Ciprofloxacin and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Hikma 200 mg/100 ml, solution for infusion
[To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for infusion contains*:*
Ciprofloxacin lactate equivalent to 2 mg ciprofloxacin.
Each vial with 100 ml contains 200 mg ciprofloxacin.
Excipient 15.4 mmol (354 mg) sodium per 100 ml of solution for infusion
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, colourless to slightly yellow solution
pH of the solution: 3.9 – 4.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Hikma is indicated for the treatment of serious and/or life-threatening infections caused by ciprofloxacin-susceptible pathogens. The following indications can be considered for treatment with Ciprofloxacin Hikma when oral therapy is not possible or not reliable:

- complicated urinary tract infections
- infections of the lower respiratory tract including pneumonia caused by aerobic gram-negative bacteria, in case of *Streptococcus pneumoniae* infections ciprofloxacin is not the substance of first choice.
- complicated skin and soft tissue infections
- osteomyelitis

Ciprofloxacin Hikma may also be administered in the treatment of acute lower respiratory tract infections caused by *Pseudomonas aeruginosa* in children aged 5-17 years with cystic fibrosis.
In case of mixed infections with anaerobes ciprofloxacin must be combined with other antibiotics effective against anaerobes.

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

4.2 Posology and method of administration

Adults:
The adult dosage is 200 - 400 mg ciprofloxacin twice daily.
In case of very serious, life-threatening or recurrent infections the dosage can be increased to 400 mg three times daily. The maximum daily dose is 1200 mg.

Osteomyelitis:
Prior to initiation of therapy, bacteriological sensitivity tests should be conducted. As with all other antibiotics, the patient should be monitored during therapy for the development of resistant strains of initially sensitive bacteria, especially *P. aeruginosa* and *S. aureus* (see the relevant statements in section

5.1). Average duration of treatment can be 4-6 weeks. If a prolonged treatment is necessary, a reassessment of treatment should be done at 2 months at the latest.

Impaired renal function:
In patients with a creatinine clearance in the range 31 - 60 ml/minute/1.73 m^2 or a serum creatinine concentration in the range 124 - 174 µmol/l, the maximum daily intravenous dose is 800 mg.
If creatinine clearance is ≤ 30 ml/minute/1.73 m^2 or the serum creatinine concentration is ≥ 175 µmol/l, the maximum daily intravenous dose is 400 mg.
In patients on haemodialysis or CAPD, the maximum daily intravenous dose is also 400 mg. On the dialysis days, the dose is given after the haemodialysis session.

Impaired hepatic function:
In case of impaired hepatic function it is not necessary to adjust the dosage.

Impaired renal and hepatic function:
Dose adjustment according to renal function. Monitoring the level of active substance in the blood provides the most reliable basis for dose adjustment.

Elderly:
Due to the higher plasma levels in the elderly it is advisable to administer a doses based on creatinine clearance and severity of disease.

Paediatric patients:
Acute lower respiratory tract infections caused by Pseudomonas aeruginosa in children and adolescents (5-17 years) with cystic fibrosis:
Twice daily intravenous administration of 15 mg/kg bodyweight, or 10 mg/kg bodyweight three times daily (maximum of 1200 mg per day).

Sequential therapy can also be used. Dosage as follows:
Twice daily intravenous administration of 15 mg/kg bodyweight, or 10 mg/kg bodyweight three times daily (maximum of 1200 mg per day), then twice daily oral administration.

The recommended duration of treatment is 10 - 14 days.

The dosage in children with impaired renal and/or hepatic function has not been investigated.

The solution for infusion should be administered over an infusion period of 60 minutes. Due to the increased risk of local reactions, higher intravenous doses in particular should only be administered via a large vein or a central line. For information on mixing with other solutions: see sections 6.2 and 6.6.

The duration of treatment depends upon the severity of infection, clinical response and bacteriological findings. Generally, acute and chronic infections (e.g. osteomyelitis and prostatitis, etc), where the causative organism is known to be sensitive to ciprofloxacin, should be treated for at least three days after the signs and symptoms of the infection have disappeared. Other specific situations such as osteomyelitis and paediatric patients are stated under **Posology**.

4.3 Contraindications

Ciprofloxacin Hikma is contraindicated in*:*

- patients with a hypersensitivity to ciprofloxacin, quinoline carboxylic acid derivatives or to any of the excipients

- children under 5 years of age. With regard to the safety and use of ciprofloxacin in children, see also section 4.4
- children and growing adolescents except for the treatment of acute pulmonary exacerbations of cystic fibrosis in children aged 5 to 17 years.
- pregnancy and lactation
- patients with a history of tendon disorder related to fluoroquinolone administration
- Concurrent administration of ciprofloxacin and tizanidine

4.4 Special warnings and precautions for use

Renal and urinary system:
Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.
Patients with pre-existent significant renal disorders should be carefully monitored to detect any deterioration in function. It should only be administered with great caution to persons with renal insufficiency, or severe dehydration.

Blood and lymphatic system:
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.

Central nervous system:
As with other fluoroquinolones, specific undesirable effects with regard to the central nervous system must be taken into account when using Ciprofloxacin Hikma. In patients with epilepsy or other lesions of the central nervous system (e.g. reduced convulsion threshold, a history of epileptic seizures, diminished cerebral blood flow, changes in brain structure or stroke), ciprofloxacin is only to be used after carefully weighing the benefits against the risk, because the possibility of central nervous side effects puts these patients at increased risk.

The undesirable effects sometimes occur already after the first administration of ciprofloxacin. Depression or psychoses lead to self-endangering behaviour in some cases. If such reactions occur, treatment with ciprofloxacin must be discontinued immediately and the treating physician informed.

Cardiac disorders:
Since ciprofloxacin is associated with very rare cases of QT prolongation (see section 4.8) caution should be exercised when treating patients at risk for torsade de pointes arrhythmia.

Children and adolescents:
As for other medicinal products in this group, ciprofloxacin has been reported to cause joint disorders in weight-bearing joints of immature animals. There are insufficient data available with regard to the use of ciprofloxacin in children and adolescents. Therefore, the use of ciprofloxacin in children is generally not recommended, except for cystic fibrosis patients (see section 4.1).

Gastrointestinal tract:
When during or after the treatment with ciprofloxacin or another fluoroquinolone severe and persistent diarrhoea occurs, pseudomembranous colitis must be taken into account (life-threatening with possibly fatal outcome). In that case the ciprofloxacin therapy must immediately be discontinued and an appropriate treatment initiated. Antiperistaltics are contraindicated. The transaminase or alkaline phosphatase concentrations may temporarily increase or cholestatic icterus might occur, especially in patients with previous liver damage.

Musculoskeletal system:

If there is any indication of tendinitis (e.g. painful swelling) the administration of ciprofloxacin or other fluoroquinolones must immediately be discontinued, the affected extremity should not be strained and a physician must be consulted. Very rarely, a partial or total rupture (in particular of the Achilles tendon) has been reported, especially in elderly patients who were previously treated systemically with glucocorticoids.
Ciprofloxacin may cause an exacerbation of Myastenia gravis symptoms. Therefore, in case of any symptom indicating an exacerbation of Myastenia gravis a physician must be consulted.

Photosensibility:
Ciprofloxacin and other fluoroquinolones may cause photosensibility. Therefore, it is recommended to avoid prolonged exposure to sunlight or UV light during treatment with ciprofloxacin. However, if this is not possible the patient is recommended to use a sun-protection cream. When photosensibility occurs the treatment must be discontinued.

Hypersensitivity:
Hypersensitivity reactions and allergic reactions occurred in some cases after the first administration of ciprofloxacin. If such reactions occur, a physician must immediately be consulted.
Anaphylactic/anaphylactoid reactions can in very rare cases develop into life-threatening shock, sometimes even after the first administration of ciprofloxacin. In that case, the ciprofloxacin treatment must be discontinued, and medical treatment for shock should be given.

Local reaction:
Local reactions have been reported after intravenous administration of ciprofloxacin. These reactions occur more frequently when the infusion time is 30 minutes or less. These may be manifested as local skin reactions, which rapidly disappear after the infusion has been completed.
Further intravenous administration is not contraindicated unless the reactions reoccur or worsen.

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

Ciprofloxacin Hikma contains 15.4 mmol (354 mg) sodium per 100 ml of solution for infusion. This has to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid
Probenecid inhibits the renal excretion of ciprofloxacin resulting in an increase in the plasma concentration of ciprofloxacin.

CYP1A2
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, tacrine, ropinirol, tizanidine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose. Determination of serum concentrations, especially of theophylline, and dose adjustments may be necessary. The interaction between theophylline and ciprofloxacin is potentially life-threatening.

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

Phenytoin

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

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.

Cyclosporine
Following concomitant administration of ciprofloxacin and cyclosporine a transient increase of the serum creatinine concentration has been observed in separate cases. Therefore, the serum creatinine concentration must be checked regularly (twice per week) in these patients.

Oral anticoagulants (e.g. warfarin)
Ciprofloxacin, like other quinolones, may enhance the effect of coumarin derivates including warfarin. In the case of concomitant administration of these products, prothrombin time (PT) or other suitable coagulation tests should be monitored. If necessary, the oral anticoagulant dose should be adjusted as appropriate.

Glibenclamide
When used simultaneously, ciprofloxacin may, in certain cases, increase the effect of glibenclamide (hypoglycaemia).

NSAIDs
Animal trials have shown that the concurrent administration of very high doses of fluoroquinolones and certain NSAIDs (but not acetylsalicylic acid) may provoke convulsions.

Mexiletine
Simultaneous administration of ciprofloxacin and mexiletine can lead to increased plasma concentrations of mexiletine.

Premedicants
It is recommended that opiate premedicants, (e.g. papaveretum) or opiate premedicants used with anticholinergic premedicants, (e.g. atropine or hyoscine) are not used concomitantly with ciprofloxacin, as the serum levels of ciprofloxacin are reduced. Co-administration of ciprofloxacin and benzodiazepine premedicants has been shown not to affect ciprofloxacin plasma levels. However, since decreased clearance of diazepam, with a prolonged half-life have been reported during co-administration of ciprofloxacin and diazepam, and in very rare cases with midazolam, careful monitoring of benzodiazepine therapy is recommended.

4.6 Pregnancy and lactation

Pregnancy
Use during pregnancy is contraindicated. There are limited data on the use of ciprofloxacin during pregnancy. Up to now, no evidence has been found of an increased risk of congenital abnormalities or other undesirable effects following use of ciprofloxacin or other quinolones during the first trimester. Teratogenic effects have not been observed in animal experimental research. In juvenile and prenatal animals exposed to quinolones effects on immature cartilage have been observed (see section 5.3). Since the risks for humans are unknown Ciprofloxacin Hikma must not be administered during pregnancy (see section 4.3).

Lactation:
Ciprofloxacin is excreted in breast milk. Due to the risk of arthropathy and other potentially severe toxicity in the infant, ciprofloxacin is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Ciprofloxacin Hikma has minor or moderate influence on the ability to drive and use machines. When undesirable effects on the central nervous system, like dizziness, occur, it is prohibited to drive a vehicle or to operate machines.

4.8 Undesirable effects

Adverse reactions have been reported in 5-14% of patients receiving ciprofloxacin. Most frequent adverse effects involve the gastro-intestinal tract and the central nervous system.

The following undesirable reactions have been observed:
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), not known (cannot be estimated from the available data)

Infections and infestations:
Uncommon: moniliasis

Blood and the lymphatic system disorders:
Uncommon: eosinophilia, leukopenia.
Rare: leukopenia (granulocytopenia), anaemia, leukocytosis, altered prothrombin values, thrombocytopenia, thrombocytemia (thrombocytosis).
Very rare: haemolytic anaemia, pancytopenia, agranulocytosis.

Immune system disorders:
Rare: oedema (peripheral, angio, facial), allergic reaction, drug fever, anaphylactoid (anaphylactic) reaction.
Very rare: pulmonary oedema in case of shock (anaphylactic; life-threatening), itching rash, serum sickness-like symptoms.

Metabolism and nutrition disorders:
Rare: hyperglycaemia.

Psychiatric disorders:
Rare: anxiety, nightmares, depression, hallucinations.
Very rare: psychotic reactions (which may progress to self-endangering behaviour).

Nervous system disorders:
Common: perverted sensation of taste (usually reversible upon discontinuation of treatment), dizziness, headache, insomnia, agitation, confusion.
Rare: taste loss (reduced taste), paraesthesia (peripheral paralgesia), tremor (shaking), convulsions**,** migraine.
Very rare: parosmia (impaired smell), anosmia (usually reversible after interruption), grand mal convulsion, abnormal (unstable) gait, intracranial hypertension, ataxia, hyperesthesia, hypertonia.

Eye disorders:
Rare: disturbed vision, diplopia, chromatopsia.

Ear and labyrinth disorders:
Rare: tinnitus, transient hearing loss (particularly high frequencies).

Cardiac disorders:
Rare: tachycardia.
In very rare cases ventricular arrhythmia, QT interval prolongation and torsades de pointes have been reported. These events were observed predominantly among patients with further risk factors for QTc prolongation.

Vascular disorders:
Uncommon: (thrombo) phlebitis.
Rare: syncope (fainting), vasodilation (heat stress).
Very rare: vasculitis (petechiae, hemorrhagic bullae, papules, crust formation).

Respiratory, thoracic and mediastinal disorders:
Rare: dyspnoea, laryngeal oedema.

Gastrointestinal disorders:
Common: nausea, diarrhoea.
Uncommon: vomiting, dyspepsia, flatulence, anorexia, abdominal pain.
Rare: pseudomembranous colitis, moniliasis (oral).
Very rare: moniliasis (gastro-intestinal), pancreatitis.

Hepato-biliary disorders:
Rare: icterus, cholestatic icterus, liver cell necrosis.
Very rare: hepatitis, liver cell necrosis (very rarely resulting in life-threatening liver function failure).

Skin and subcutaneous tissue disorders:
Common: rash.
Uncommon: pruritis, papillo-macular rash, urticaria.
Rare: photosensibility, erythema multiforme and erythema nodusum.
Very rare: erythema nodosum, erythema multiforme (minor), Stevens-Johnson syndrome, epidermal necrolysis (Lyell Syndrome), petechia.

Musculoskeletal and connective tissue disorders:
Uncommon: arthralgia (joint pain).
Rare: myalgia (muscular pain), joint disorder (swollen joints).
Very rare: tendinitis (in particular of the Achilles tendon), partial or total tendon ruptures (in particular of the Achilles tendon), worsening of the symptoms of myasthenia, muscular pains, inflammation of tendon sheaths (tenosynovitis).

Renal and urinary disorders:
Rare: acute renal failure, impaired renal function, vaginal moniliasis, haematuria, crystalluria, interstitial nephritis.

General disorders and administration site conditions:
Uncommon: asthenia (general sensation of weakness, fatigue), injection site reactions.
Rare: transpiration.

Investigations:
Uncommon: increase of blood creatinine levels, increased blood urea; abnormal liver function test results (increased SGOT and SGPT), bilirubinemia and increased alkaline phosphatase.

Very rare: increment of amylase/lipase levels.

Others:
Uncommon: pulmonary embolism, dyspnoea, pulmonary oedema, epistaxis, haemoptysis and hiccough.
Very rare: asthenia, a transient impairment of kidney function to transient renal failure, photosensitivity (see Section 4.4).

4.9 Overdose

In acute and extreme overdosage, reversible kidney damage is seen. An overdose of 12 g has been reported to lead to mild symptoms of toxicity. Symptoms of overdose may include dizziness, tremor, headaches, tiredness, seizures, hallucinations, confusion, gastrointestinal upset, liver and kidney abnormalities, crystalluria, haematuria.
The patient should be monitored closely and treated symptomatically with supportive measures. Adequate hydration must be ensured. At haemodialysis or peritoneal dialysis only a modest amount of ciprofloxacin (less than 10%) is eliminated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial quinolones, ATC code: J01MA02

Mode of action:
Ciprofloxacin has a rapid bactericidal effect, both in the growth phase and in the rest phase. During the growth phase of bacteria, a partial rolling up and unfolding of chromosomes takes place. The enzyme DNA-gyrase plays a crucial role in this process. Ciprofloxacin inhibits DNA-gyrase, resulting in inhibition of DNA synthesis.
Ciprofloxacin is effective *in vitro* against a large number of Gram-negative aerobic bacteria including *P. aeruginosa*. It is also effective against Gram-positive organisms, such as staphylococci and streptococci. Anaerobes are generally less sensitive.

Mechanism of resistance:
Resistance to ciprofloxacin develops in stages through genomic mutations (multiple-step type). Transferable plasmid-mediated quinolone resistance associated with qnr has been detected in quinolone-resistant clinical strains of E.coli and Klebsiella spp. As a result of its mechanism of action, ciprofloxacin does not show cross-resistance with other important, chemically different groups of substances such as beta-lactam antibiotics, aminoglycosides, tetracyclines, macrolides and polypeptides, sulphonamides, trimethoprim and nitrofurantoine.
Within the class of quinolones cross-resistance has been observed. Development of resistance to ciprofloxacin and other fluoroquinolones has been observed in staphylococci, especially methicillin-resistant S. aureus, P. aeruginosa, E.coli and E. faecalis (see the sensitivity table).

Especially patients undergoing long-term treatment (e.g. in cystic fibrosis, osteomyelitis), or patients who are extremely susceptible to infections (e.g. in selective prophylaxis in certain groups of neutropenic patients, artificial ventilation) show the highest risk. The percentage of resistant strains can be subject to great local variation. Regular determination of resistance is therefore recommended.

Breakpoints:
According to EUCAST the following breakpoints for aerobic bacteria have been defined for ciprofloxacin:

- *Enterobacteriaceae*: ≤ 0.5 µg/ml for susceptible, > 1 µg/ml for resistant;
- *Pseudomonas* spp. ≤ 0.5 µg/ml for susceptible, > 1 µg/ml for resistant;

- *Acinetobacter* spp. ≤ 1 µg/ml for susceptible, > 1 µg/ml for resistant;
- *S. pneumonia* ≤ 0.125 µg/ml for susceptible, > 2 µg/ml for resistant;
- *Staphylococcus* spp. ≤ 1 µg/ml for susceptible, > 1 µg/ml for resistant;
- *H. influenza* and *M. catarrhalis* ≤ 0.5 µg/ml for susceptible, > 0.5 µg/ml for resistant.
-

Non-species related breakpoints are ≤ 0,5 µg/ml for susceptible, and > 1 µg/ml for resistant organisms.

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-negative aerobe species
Citrobacter spp.
Citrobacter freundii
Enterobacter cloacae
Haemophilus influenzae
Moraxella spp.
Moraxella catarrhalis
Morganella morganii
Proteus spp.
Proteus mirabilis
Proteus vulgaris
Serratia liquefaciens
Serratia marcescens
Species for which acquired resistance may be a problem
Gram-positive aerobes
Coagulase-negative Staphylococcus
Enterococcous faecalis
*MRSA**
Staphylococcus aureus
Staphylococcus aureus (methicillin susceptible)
Streptococcus spp.
Streptoococus agalactiae
Streptococcus pneumoniae
S. pneumoniae PEN-R
Streptococcus pyogenes
Gram-negative aerobes
Acinetobacter spp.
Acinetobacter baumannii
Enterobacter spp.
Enterobacter aerogenes
Enterobacter spp. Amp-C producing
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Pseudomonas aeruginosa
Inherently resistant organisms
Gram-positive aerobes
Enterococcus faecium
Staphylococcus epidermidis
Staphylococcus haemolyticus
Gram-negative aerobes

E. coli multi-resistant
Providencia spp.

** 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
MRSA: Methicillin-resistant Staphylococcus aureus

5.2 Pharmacokinetic properties

Absorption:
Ciprofloxacin is rapidly and effectively absorbed after oral administration. The peak plasma concentration is reached 0.5 - 2 hours after taking 50 - 1000 mg p.o. and varies from 0.3 - 5.9 mg/l. There is a linear correlation between dose on the one hand and plasma concentration and AUC on the other. The bioavailability of ciprofloxacin after oral administration is between 70 % and 85 %.
The bioavailability is lower if antacids that contain aluminium and/or magnesium hydroxide, and calcium and iron salts are used concomitantly.
No accumulation occurs on repeated administration (twice daily). Twelve hours after i.v. administration of 200 mg the plasma concentration is still higher than the MIC values of the majority of clinically relevant pathogens (approximately 0.1 µg/ml).

Distribution:
In steady-state conditions the apparent distribution volume of ciprofloxacin is situated between 1,7 and 2,7 l/kg. This relatively high distribution volume indicates an effective tissue and fluid penetration. This applies to gall, kidney, gall bladder and liver tissue.
Concentrations in pulmonary tissue, gynaecological tissue and prostate tissue and fluid were also significantly higher than the serum concentration.
The ciprofloxacin concentration in blister fluid, lymph, nasal secretion, peritoneal fluid, saliva and fatty tissue is approximately half of the serum concentration. The ciprofloxacin concentration in the sputum consists of 50-70% of the serum concentration.
Animal experiments have shown that ciprofloxacin passes the placenta and is excreted in breast milk.
The plasma protein binding of ciprofloxacin is situated between 16% and 28% and is not dependent on the concentration and pH (determined by means of ultrafiltration).

Biotransformation:
Ciprofloxacin is mainly excreted unchanged. Part of it is converted into desethylene-, sulpho-, oxo- and formylciprofloxacin. All metabolites are active, but in a lesser degree than ciprofloxacin.

Elimination:
After oral administration ciprofloxacin is excreted unchanged for approx. 70% and after i.v. administration for approx. 77%. After oral administration 45% is excreted unchanged in the urine and 25% is excreted in the faeces. After i.v. administration 62% is excreted unchanged in the urine and 15% is excreted in the faeces. After oral administration 19% and after i.v. administration 12% of ciprofloxacin is excreted in the urine and faeces in the form of metabolites. A larger number of metabolites after oral administration indicates some degree of first-pass metabolism, mainly forming sulphociprofloxacin.
The total body clearance of ciprofloxacin is independent of the dose and remains unchanged in case of multiple administrations. The renal clearance constitutes 60%-70% of the total body clearance and is approximately 3 times higher than the creatinine clearance. The renal clearance occurs through glomerular filtration and active tubular secretion.
The elimination half-life of ciprofloxacin after single or multiple oral dosage is between 3.4 and 6.9 hours. After single and multiple i.v. dosage the elimination half-life is between 3 – 4.6 hours.

Characteristics in patients:
In patients with severely impaired renal function (creatinine clearance <30 ml/min) the elimination half-life may be prolonged by a factor of 2.

The elimination half-life of ciprofloxacin does not change with age.

The pharmacokinetics of ciprofloxacin in children with cystic fibrosis differs from that in children without cystic fibrosis, and dosing recommendations are only applicable for children with cystic fibrosis. Oral administration of 20 mg/kg twice daily to children with cystic fibrosis gives an exposure that is comparable to that in adults following an oral dose of 750 mg twice daily.

5.3 Preclinical safety data

Like with other gyrase inhibitors, ciprofloxacin may induce joint damage during the growth phase of juvenile animals.
Ciprofloxacin is potentially neurotoxic and causes reversible defects of the testes in case of higher dosage. Mutagenicity of ciprofloxacin has not been indicated in mutagenicity studies. However, like a number of other quinolones ciprofloxacin is phototoxic in animals in exposure values relevant to humans. The phototoxic, photomutagenic and photocarcinogenic potential of ciprofloxacin is comparable to that of other gyrase inhibitors. Other preclinical effects were observed only at exposures that were sufficiently in excess of the maximum human exposure so that concern for human safety is negligible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid (E 270)
Sodium chloride
Hydrochloric acid (E 507) for pH adjustment
Water for injections

6.2 Incompatibilities

Ciprofloxacin Hikma cannot be mixed with solutions that are not stable at a pH of approximately 4.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not refrigerate or freeze.
Keep the vial in the outer carton until time of use in order to protect from light.

6.5 Nature and contents of container

Type I, clear glass vial, fitted with a chlorobutyl rubber stopper and aluminium flip-off caps.
Pack sizes: 1.5 10 or 20 vials.

6.6 Special precautions for disposal

Use only clear solutions and undamaged containers.
For single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.
To be used immediately after the vial is opened.

Ciprofloxacin Hikma is compatible with physiological sodium chloride solution, Ringer's solution, Ringer's lactate solution, 50 mg/ml (5 %) or 100 mg/ml (10 %) glucose solution and 50 mg/ml (5 %) glucose solution with 2.25 mg/ml (0.225 %) or 4.5 mg/ml (0.45 %) sodium chloride solution and 10% fructose solution. Compatibility with these solutions has been proven in ciprofloxacin concentrations of 1 mg/ml. Chemical and physical in-use stability has been demonstrated immediately after dilution, after 24 hours at 2-8°C and after 24 hours at room temperature. Unless compatibility is proven, the solution for infusion should always be administered separately.
The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear.

7. MARKETING AUTHORISATION HOLDER

Hikma Farmacêutica (Portugal), Lda.
Estrada do Rio da Mó n.º 8, 8A e 8B – Fervença
2705-906 Terrugem SNT
Portugal
Tel.: +351 219 608 410
Fax: +351 219 615 102
e-mail: geral@hikma.pt

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

.

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Hikma 200 mg/100 ml, solution for infusion
[To be completed nationally]
ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml solution for infusion contains : Ciprofloxacin lactate equivalent to 2 mg ciprofloxacin.
Each vial with 100 ml contains 200 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Lactic acid (E270), sodium chloride, hydrochloric acid (E507) and water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

See enclosed leaflet.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton until time of use in order to protect from light.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution and the vial should be adequately disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hikma Farmaceutica (Portugal), Lda.
Estrada do Rio da Mó, 8, 8A e 8B - Fervença
2705-906 Terrugem SNT
Portugal
Tel.: +351 219 608 410
Fax: +351 219 615 102
geral@hikma.pt

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch nr.{xxxxxx}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ciprofloxacin Hikma 200 mg/100 ml, solution for infusion
[To be completed nationally]
ciprofloxacin
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYY}

4. BATCH NUMBER

Batch nr. {xxxxxx}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Presentation of 200 mg/100 ml: 100 ml

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Hikma 200 mg/100 ml, solution for infusion
[To be completed nationally]

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 HIKMA IS AND WHAT IT IS USED FOR

Ciprofloxacin Hikma is an antibiotic.

Ciprofloxacin Hikma is used for the treatment of severe and/or life-threatening infections caused by ciprofloxacin-sensitive microorganisms. The following infections may be treated intravenously (via the blood) with Ciprofloxacin Hikma:
- complicated urinary tract infections
- certain lower respiratory tract infections including pneumonia
- complicated skin and soft tissue infections
- bone infections.

Children and Adolescents
Ciprofloxacin Hikma can also be used for the treatment of acute lower respiratory tract infections caused by *Pseudomonas aeruginosa* bacteria in children and adolescents aged 5-17 years with cystic fibrosis (also called *mucoviscidosis*), a hereditary disease of specific glands. It affects the lungs, sweat glands and the digestive system causing chronic respiratory and digestive problems.

2. BEFORE YOU USE CIPROFLOXACIN HIKMA

Do NOT use Ciprofloxacin Hikma:
- If you have known allergic reaction (*hypersensitivity*) to ciprofloxacin or any of the other ingredients of Ciprofloxacin Hikma or other medicines of the quinolone type
- In children aged below 5 years
- In children and growing adolescents except for the treatment of acute lower respiratory tract infections caused by *Pseudomonas aeruginosa* bacteria in children and adolescents aged 5-17 years with cystic fibrosis
- In patients with a history of tendon disorder related to fluoroquinolone administration
- If you are pregnant or wish to become pregnant
- If you are breast-feeding.
- If Ciprofloxacin Hikma and tizanidine (used to treat muscle spasms) are given at the same time.

Take special care with Ciprofloxacin Hikma
You should consult your doctor if one of the precautions and warnings mentioned below are or were applicable to you in the past.

Before starting treatment *- if you suffer or have suffered from one of the following diseases:*
- convulsions (seizures), epilepsy or another brain disease, for example decreased blood circulation in the brain, stroke or increased sensitivity to convulsions, since possible side effects of ciprofloxacin may cause damage to the brain.
- life-threatening increase heart rate (torsade de pointes). If you suffer from this disease, you should consult your doctor.
- myastenia gravis (a particular type of muscle weakness). Ciprofloxacin can exacerbate the symptoms of this disease. In case of any symptom indicating an exacerbation of myastenia gravis, you should therefore consult your doctor.
- liver impairment in the past. When symptoms occur, such as yellowing of the skin or whites of the eyes, you should immediately consult your doctor.
- significant renal impairment. Your doctor will check your renal function carefully.
- glucose-6-phosphate dehydrogenase defect (hereditary disease of the red blood cells based on a defect in an enzyme). If you or someone in your family suffers from this disease, you should consult your doctor. An extensive destruction of red blood cells (haemolytic reactions) may occur, causing anaemia. Signs of anaemia are a feeling of weakness and in more severe cases breathlessness and pale skin.

During or after treatment *- if one of the following conditions occurs:*
- feeling depressed or confused after administration of Ciprofloxacin Hikma. In this case you should immediately consult your doctor.
- temporary pain and inflammation of the tendons, in particular of the Achilles tendon. This medicine may cause these side effects, particularly if you are older or take a medicine of the so-called steroid group, such as hydrocortisone.
- If you experience these symptoms you should immediately consult your doctor and rest the respective leg.
- severe and continuous diarrhoea during treatment, possibly with blood and mucus. In this case you should immediately consult your doctor, since you may have a severe inflammation of the large intestine (pseudo membranous colitis). This condition is life-threatening and may have a fatal outcome.
- increased skin sensitivity to sunlight or UV light. You should avoid long exposure to strong sunlight, sunlamps or other sources of UV radiation.
- If exposure to sunlight or UV light is inevitable you should use sun cream to protect yourself.
- If nevertheless complaints occur, such as fever, rash, itching, small red spots on the skin, you should consult your doctor since the treatment may need to be discontinued.
- allergic reactions after the first administration of this medicine. In this case you should immediately consult your doctor. Signs of these reactions are: a sharp drop in blood pressure, paleness, restlessness, weak/rapid pulse, clammy skin, dizziness. In very rare cases these allergic reactions may lead to life-threatening shock.
- local reactions after administration of this medicine. These reactions may occcur particularly when the infusion time is 30 minutes or less. They may take the form of local skin reactions, such as reddening of the skin, irritation or pain, which usually disappear quickly after termination of the infusion. If these reactions recur or exacerbate during a following infusion no further infusions should be administered.
- crystalluria (presence of crystals in the urine with discomfort when passing urine). In this case consult your doctor as your urine needs to be tested. Furthermore, you should drink a sufficient amount of liquid (about 1.5 – 2 litres daily).
- *Mycobacerium tuberculosis* test. Please inform your doctor when under treatment with Ciprofloxacin Hikma as the result of this test may be false.

Using other medicines
If Ciprofloxacin Hikma and one of the following medicines are given at the same time, special care should be taken:

- theophylline (used to treat asthma), clozapine (used to treat schizophrenia), tacrine (used to treat symptoms of Alzheimer´s disease), ropinirol (used to treat Parkinson disease) and tizanidine (used to treat muscle spasms).

If you use one of these medicines together with ciprofloxacin you will be monitored for signs of overdose. The above-mentioned substances are converted by a specific enzyme (CYP1A2). Ciprofloxacin inhibits this enzyme. Therefore the amount of these other medicines may rise in the blood.

- certain anti-inflammatory agents (e.g. ibuprofen, naproxen, but not acetylsalicylic acid), if ciprofloxacin is given in very high doses. This may cause epileptic seizures.
- cyclosporine (used to prevent rejection reactions after organ transplantations).

In this case the kidney function must be frequently (twice per week) monitored.

- oral anticoagulants (used to prevent blood from clotting, e.g. warfarin). This may lead to a prolongation of the bleeding time. Therefore the bleeding time should be monitored.
- glibenclamide (used to treat diabetes). This may increase the effect of glibenclamide (too low blood sugar level).
- probenecid (used to treat gout). The ciprofloxacin level in the blood can be increased.
- phenytoin (used to treat epilepsy). The blood level of this medicine can be increased or reduced.
- caffeine (used as a stimulant), pentoxifylline (used to treat circulatory disorders in the limbs) and mexiletine (used to treat irregular heart beat). The blood level of these medicines can be increased.
- methotrexate (used to treat cancer or suppress the immune system). Your doctor will monitor you for signs of methotrexate overdose.
- Ciprofloxacin may inhibit the excretion of methotrexate via the kidney, causing an increased methotrexate level in the blood.
- Pre-medicants (used before anaesthesia induction): it is recommended that opiate pre-medicants, (e.g. papaveretum) or opiate pre-medicants used with anticholinergic pre-medicants, (e.g. atropine or hyoscine) are not used concomitantly with ciprofloxacin, as the serum levels of ciprofloxacin are reduced. Co-administration of ciprofloxacin and benzodiazepine pre-medicants has been shown not to affect ciprofloxacin plasma levels. However, since decreased clearance of diazepam, with a prolonged half-life have been reported during co-administration of ciprofloxacin and diazepam, and in very rare cases with midazolam, careful monitoring of benzodiazepine therapy is recommended.

If one of the above-mentioned situations is applicable to you, your doctor may decide to prescribe you another medicine or to adjust the dose of Ciprofloxacin Hikma or the other medicine.

It is advisable never to use several medicines at the same time without consulting your doctor first.

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

Pregnancy and breast-feeding
You must not be given Ciprofloxacin Hikma during pregnancy. You should consult your doctor if you are pregnant or wish to become pregnant.
Ask your doctor or pharmacist for advice before taking any medicine.

Ciprofloxacin is passed into human breast milk. You must not breast-feed your child during treatment with ciprofloxacin, due to the risk of malformation of joint cartilage and other harmful effects in the breast-fed infant. You should consult your doctor if you are breast-feeding your child.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Ciprofloxacin can reduce your attention. If you suffer from dizziness, do not drive or operate machines, which require your full concentration.

Important information about some of the ingredients of Ciprofloxacin Hikma
If you are on a low-sodium diet, take into account that 100 ml of Ciprofloxacin Hikma contains 15.4 mmol (equivalent to 354 mg) sodium.

3. HOW TO USE CIPROFLOXACIN HIKMA

Dosage
The Ciprofloxacin Hikma dosage is based on the severity and type of the infection, the sensitivity of the pathogen(s), your age, weight and kidney function.
The usual dose in adults is 200-400 mg of ciprofloxacin twice daily.
In case of very severe infections the dose can be increased up to a maximum daily dose of 1200 mg (400 mg thrice daily).

Children and adolescents
For the treatment of acute pulmonary infections caused by *Pseudomonas aeruginosa* bacteria in children and adolescents (5-17 years) with cystic fibrosis 15 mg of ciprofloxacin per kg body weight is administered twice daily or 10 mg ciprofloxacin per kg body weight is administered three times daily (maximum 1200 mg daily).

Dosage adjustment
If you are older than 65 years your doctor may prescribe you a dose based on your kidney function and severity of disease.

If you have kidney problems you should inform your doctor. He/she may find it necessary to adjust your dose due to a reduced kidney function.

Method and route of administration
Ciprofloxacin Hikma should be administered via a short-term intravenous infusion (infusion into a vein) over 30 to 60 minutes.

Duration of treatment
The duration of treatment with Ciprofloxacin Hikma is based on the severity of the infection, the effect of the treatment and the sensitivity of the pathogen(s).
The treatment should be continued for at least three days after the signs of the infection have disappeared.
The treatment of acute pulmonary infections in children and adolescents with cystic fibrosis will take 10-14 days.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin Hikma can cause side effects, although not everybody gets them.
Side effects have been reported in 5-14% of patients receiving ciprofloxacin.
Most frequent side effects affect the stomach and intestine, the nervous system and the skin and connective tissue.
For more details regarding some of the side effects please see Section 2, ‘Take special care with Ciprofloxacin Hikma- During or after treatment’.

The frequency of side effects is classified into the following categories:

Very common	in more than 1 in 10 patients
Common	in more than 1 in 100 patients, but less than 1 in 10 patients
Uncommon	in more than 1 in 1,000 patients, but less than 1 in 100 patients
Rare	in more than 1 in 10,000 patients, but less than 1 in 1,000 patients
Very rare	in less than 1 in 10,000 patients, including isolated reports

Common:
- distorted sensation of taste (usually reversible upon discontinuation of treatment), dizziness, headache, difficulty in sleeping (insomnia), restlessness (agitation), confusion
- nausea, diarrhoea
- rash

Uncommon:
- fungal infection (mobilises)
- increase in eosinophilic cells (eosinophilia), reduction in white blood cells (leucopenia) which makes infections more likely
- inflammation of a vein related to a blood clot (thrombophlebitis); the vein is often sensed as a tender hard strand covered with red skin
- vomiting, digestive disorders, gassiness (flatulence), loss of appetite, abdominal pain
- itching (pruritus), spot-shaped rash (maculopapular rash), hives (urticaria)
- joint pain (arthralgia)
- general sensation of weakness, fatigue (asthenia), irritation or pain at the injection site
- increase of the creatinine or urea level in the blood, abnormal liver function test results, bile pigment in the blood (bilirubinaemia) and increased blood level of a certain enzyme (alkaline phosphatase)
- pulmonary embolism, laboured breathing (dyspnoea), pulmonary oedema, nosebleed (epistaxis), coughing up blood (haemoptysis) and hiccough.

Rare:
- reduction in red blood cells (anaemia), increase in white blood cells (leucocytosis), alteration of the prothrombin (coagulation factor) values, reduction in blood platelets (thrombocytopenia) with bruises and tendency to bleed, increase in blood platelets (thrombocytosis)
- swelling of the limbs and face (peripheral oedema, facial oedema), sudden swelling of the face or throat with difficulties in breathing and/or itching and rash, often as an allergic reaction (angioneurotic oedema), allergic reactions, fever due to the administration of the medicine, serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction)
- increased blood sugar level (hyperglycaemia)
- anxieties, nightmares, severe depression, seeing things or hearing voices that do not exist (hallucinations)
- reduced taste, altered sensation (paraesthesia), shaking (tremor), spasms/ convulsions (seizures), severe headache (migraine)
- altered vision such as double vision (diplopia) and seeing all objects in a certain colour (chromatopsia)
- ringing in the ear (tinnitus), transient hearing loss (particularly high frequencies)
- increased heart rate (tachycardia)
- fainting (syncope), widening of blood vessel (vasodilation)
- shortness of breath (dyspnoea), swelling of the voice box (larynx) with difficulties in breathing (larynx oedema)
- severe and continuous diarrhoea, possibly with blood and mucus, due to a severe inflammation of the large intestine (pseudo membranous colitis), fungal infection in the mouth (oral moniliasis)
- yellowing of the skin or whites of the eyes (icterus), icterus due to a condition where the bile can not flow normally from the liver (cholestatic icterus), liver cell necrosis
- increased sensitivity to light (photosensitivity), erythema multiforme and erythema nodusum
- muscular pain (myalgia), joint disorder (swollen joints)
- acute kidney failure, abnormal kidney function, vaginal secretion due to a fungal infection (vaginal moniliasis), blood in the urine (haematuria), presence of crystals in the urine with discomfort when passing urine (crystalluria), infection of the kidney with blood in the urine, fever and pain in the side (interstitial nephritis)

- perspiration

Very rare:
- reduction in red blood cells due to extensive destruction of these cells (haemolytic anaemia), severe reduction in blood cells (pancytopenia), severe reduction in white blood cells characterised by sudden high fever, very sore throat and mouth ulcers (agranulocytosis)
- a life-threatening condition characterised by a sharp drop in the blood pressure, paleness, restlessness, weak/quick pulse, clammy skin, dizziness as a result of severe allergy to this medicine (anaphylactic shock), itching rash, fever, joint swellings, muscle pains, rash (symptoms similar to those occurring in a disease called serum sickness)
- disturbed control of own behaviour and actions (psychotic reactions which may progress to self-endangering behaviour)
- smell disorder (parosmia), loss of smell (anosmia, the smell usually returns after termination of treatment), convulsions (grand mal convulsion), abnormal (unstable) gait, increased pressure in the head (intracranial hypertension), lack of coordination (ataxia), increased sensitivity to stimulation (hyperaesthesia), stiffness (hypertonia)
- irregular heart beat (ventricular arrhythmia), abnormal electrocardiogram heart tracing, life-threatening increased heart rate (torsade de pointes). These side effects occur predominantly in patients at risk for certain heart disorders.
- inflammation of blood vessels (vasculitis) characterised by: small spots caused by bleeding in the skin (petechiae), bloody blisters (haemorrhagic bullae), skin nodes (papules), formation of eschar (dead tissue that sheds (sloughs-off) from healthy skin)
- fungal infection in the gastrointestinal system (gastrointestinal moniliasis), pancreas inflammation (pancreatitis)
- liver inflammation (hepatitis), destruction of liver tissue (liver cell necrosis, very rarely resulting in life-threatening liver failure)
- rash with red (moist) irregular spots (erythema (exsudativum) multiforme), tender bluish red bumps in the skin (erythema nodosum), severe condition with (high) fever, red spots on the skin, joint pains and/or eye infection (Stevens-Johnson syndrome), severe condition with fever and blisters on the skin/peeling of the skin (Lyell syndrome), small purplish red spot (petechia)
- inflammation of the tendons (tendinitis, in particular of the Achilles tendon), partial or total tendon ruptures (in particular of the Achilles tendon), exacerbation of the symptoms of myasthenia gravis (a particular type of muscle weakness), muscular pains, inflammation of tendon sheaths (tenosynovitis)
- increased blood level of amylase (enzyme that breaks down starch) and lipase (enzyme that breaks down fats).
- weakness (asthenia), a transient impairment of kidney function to transient renal failure, photosensitivy.

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 HIKMA

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Hikma after the expiry date which is stated on the packaging after "Exp". The expiry date refers to the last day of that month.

- Do not refrigerate or freeze.
- Keep the vial in the outer carton until time of use in order to protect from light.

6. FURTHER INFORMATION

What Ciprofloxacin Hikma contains

The active substance is ciprofloxacin lactate.
Each vial of 100 ml contains 200 mg of ciprofloxacin.

The other ingredients are lactic acid (E270), sodium chloride, hydrochloric acid (E507) for pH adjustment and water for injections.

What Ciprofloxacin Hikma looks like and contents of the pack
Ciprofloxacin Hikma is a sterile, clear and colourless to slightly yellow solution for infusion.
It is contained in a type I, clear, colourless glass vial containing 100 ml solution.

Marketing Authorisation Holder and Manufacturer

Hikma Farmacêutica (Portugal), Lda.
Estrada do Rio da Mó n.º 8, 8A e 8B – Fervença
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For any information about this medicine, please contact the the Marketing Authorisation Holder.

This medicinal product is authorised in the Member States of EEA under the following names:
Austria – Ciprofloxacin Hikma 200mg/100ml Infusionslösung
Germany – Ciprofloxacin Hikma 200mg/100ml Lösung zur Intravenösen Anwendung
Ireland – Ciprofloxacin Hikma 200mg/100ml Solution for Infusion
Italy – Ciprofloxacin Hikma 200mg/100ml Soluzione per Infusione Endovenosa
United Kingdom – Ciprofloxacin Hikma 200mg/100ml Solution for Infusion
The Netherlands – Ciprofloxacine Hikma 200mg/100ml Oplossing voor Intraveneuze Infusie

This leaflet was last approved in {MM/YYYY}.

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

Use only clear solutions and undamaged containers. To be used immediately after the vial is opened. For single use only.
Any unused solution and the vial should be adequately disposed of in accordance with local requirements.

Ciprofloxacin Hikma is compatible with isotonic sodium chloride solution, Ringer's solution, Ringer's lactate solution, 50 mg/ml (5 %) or 100 mg/ml (10 %) glucose solution and 50 mg/ml (5 %) glucose solution with 2.25 mg/ml (0.225 %) or 4.5 mg/ml (0.45 %) sodium chloride solution and 10% fructose solution. Compatibility with these solutions has been proven in ciprofloxacin concentrations of 1 mg/ml. Chemical and physical in-use stability has been demonstrated immediately after dilution, after 24 hours at 2-8°C and after 24 hours at room temperature. Unless compatibility is proven, the solution for infusion should always be administered separately.
The diluted solution should be inspected visually for particulate matter and discoloration prior to administration. The diluted solution should be clear.