ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Name	Strength	Pharmaceutical Form	Route of administration	Content (concentration)
Netherlands	Fresenius Kabi Nederland B.V. Postbus 2379 NL-5202 CJ´s Hertogenbosch Netherlands Tel-No.: 0800 022 1905 Fax.No.: 0800 022 8295		Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Netherlands	Fresenius Kabi Nederland B.V. Postbus 2379 NL-5202 CJ´s Hertogenbosch, Netherlands Tel-No.: 0800 022 1905 Fax.No.: 0800 022 8295		Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Netherlands	Fresenius Kabi Nederland B.V. Postbus 2379 NL-5202 CJ´s Hertogenbosch, Netherlands Tel-No.: 0800 022 1905 Fax.No.: 0800 022 8295		Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml

Austria	Fresenius Kabi Austria GmbH, Hafnerstraße 36, A-8055 Graz, Austria Tel-No.: 0043 316 249 524 Fax.No.: 0043 316 249 270	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Austria	Fresenius Kabi Austria GmbH, Hafnerstraße 36, A-8055 Graz, Austria Tel-No.: 0043 316 249 524 Fax.No.: 0043 316 249 270	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Austria	Fresenius Kabi Austria GmbH, Hafnerstraße 36, A-8055 Graz, Austria Tel-No.: 0043 316 249 524 Fax.No.: 0043 316 249 270	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Belgium	Fresenius Kabi N.V. Molenberglei 7 B-2627 Schelle, Belgium Tel-No.: 0032 3 880 5024 Fax.No.: 0032 3 880 2888	Ciprofloxacin Fresenius Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Belgium	Fresenius Kabi N.V.Molenberglei 7B-2627 Schelle, Belgium Tel-No.: 0032 3 880 5024 Fax.No.: 0032 3 880 2888	Ciprofloxacin Fresenius Kabi 400 mg/200 ml,solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml

Cyprus	Fresenius Kabi Hellas A.E. 354 Messoghoin Avenue GR 153-41 Agia Paraskevi Attica, Greece Tel-No.: 0030 210 654 2909 Fax.No.: 0030 210 654 8909	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Cyprus	Fresenius Kabi Hellas A.E. 354 Messoghoin Avenue GR 153-41 Agia Paraskevi Attica, Greece Tel-No.: 0030 210 654 2909 Fax.No.: 0030 210 654 8909	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Cyprus	Fresenius Kabi Hellas A.E. 354 Messoghoin Avenue GR 153-41 Agia Paraskevi Attica, Greece Tel-No.: 0030 210 654 2909 Fax.No.: 0030 210 654 8909	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Czech Republic	Fresenius Kabi Nederland B.V. Postbus 2379 NL-5202 CJ´s Hertogenbosch, Netherlands Tel-No.: 0800 022 1905 Fax.No.: 0800 022 8295	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml

Czech Republic	Fresenius Kabi Nederland B.V. Postbus 2379 NL-5202 CJ´s Hertogenbosch, Netherlands Tel-No.: 0800 022 1905 Fax.No.: 0800 022 8295	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Czech Republic	Fresenius Kabi Nederland B.V. Postbus 2379 NL-5202 CJ´s Hertogenbosch, Netherlands Tel-No.: 0800 022 1905 Fax.No.: 0800 022 8295	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Germany	Fresenius Kabi Deutschland GmbH,D-61346 Bad Homburg v.d.H.,GermanyTel-No.: 0049 6172 686 0Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Germany	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml

Germany	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Denmark	Fresenius Kabi AB SE-75174 Uppsala Sweden Tel-No.: 0046 18 644 000 Fax.No.: 0046 18 644 013	Ciprofloxacin Fresenius Kabi 2 mg/ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml, 400 mg/200 ml
Greece	Fresenius Kabi Hellas A.E. 354 Messoghoin Avenue GR 153-41 Agia Paraskevi Attica, Greece Tel-No.: 0030 210 654 2909 Fax.No.: 0030 210 654 8909	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Greece	Fresenius Kabi Hellas A.E. 354 Messoghoin Avenue GR 153-41 Agia Paraskevi Attica, Greece Tel-No.: 0030 210 654 2909 Fax.No.: 0030 210 654 8909	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml

Greece	Fresenius Kabi Hellas A.E. 354 Messoghoin Avenue GR 153-41 Agia Paraskevi Attica, Greece Tel-No.: 0030 210 654 2909 Fax.No.: 0030 210 654 8909	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Spain	Fresenius Kabi España S.A.c./ Marina 16-18, planta 17,E-08005 Barcelona,SpainTel-No.: 0034 93 225 6580Fax.No.: 0034 93 225 6573	Ciprofloxacin Kabi 2 mg/ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml, 400 mg/200 ml
Finland	Fresenius Kabi AB SE-75174 Uppsala Sweden Tel-No.: 0046 18 644 000 Fax.No.: 0046 18 644 013	Ciprofloxacin Fresenius Kabi 2 mg/ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml, 400 mg/200 ml
Hungary	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml

Hungary	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Italy	Fresenius Kabi Italia S.r.L. via Camagre 41 I-37063 Isola della Scala (VR), Italy Tel-No.: 0039 0456649311 Fax.No.: 0039 0456649404	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Italy	Fresenius Kabi Italia S.r.L. via Camagre 41 I-37063 Isola della Scala (VR), Italy Tel-No.: 0039 0456649311 Fax.No.: 0039 0456649404	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Italy	Fresenius Kabi Italia S.r.L. via Camagre 41 I-37063 Isola della Scala (VR), Italy Tel-No.: 0039 0456649311 Fax.No.: 0039 0456649404	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml

Poland	Fresenius Kabi Deutschland GmbH,D-61346 Bad Homburg v.d.H.,GermanyTel-No.: 0049 6172 686 0Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
Poland	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Poland	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Portugal	Fresenius Kabi Pharma Portugal Lda., Avenida do Forte 3, Edifício Suécia IV, Piso 3, 2794-039 Carnaxide, Portugal Tel-No.: 00351 21424 1284 Fax.No.: 00351 21424 1290	Ciprofloxacin Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml

Portugal	Fresenius Kabi Pharma Portugal Lda., Avenida do Forte 3, Edifício Suécia IV, Piso 3, 2794-039 Carnaxide, Portugal Tel-No.: 00351 21424 1284 Fax.No.: 00351 21424 1290	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Portugal	Fresenius Kabi Pharma Portugal Lda., Avenida do Forte 3, Edifício Suécia IV, Piso 3, 2794-039 Carnaxide, Portugal Tel-No.: 00351 21424 1284 Fax.No.: 00351 21424 1290	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
Sweden	Fresenius Kabi AB SE-75174 Uppsala Sweden Tel-No.: 0046 18 644 000 Fax.No.: 0046 18 644 013	Ciprofloxacin Fresenius Kabi 2 mg/ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml, 400 mg/200 ml
Slovak Republic	Fresenius Kabi Deutschland GmbH,D-61346 Bad Homburg v.d.H.,Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 100 mg/50 ml,solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml

Slovak Republic	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml
Slovak Republic	Fresenius Kabi Deutschland GmbH, D-61346 Bad Homburg v.d.H., Germany Tel-No.: 0049 6172 686 0 Fax.No.: 0049 6172 686 7332	Ciprofloxacin Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml
United Kingdom	Fresenius Kabi Limited Cestrian Court, Eastgate Way Manor Park, Runcorn Cheshire WA7 1NT, UK, Tel-No.: 0044 1928 594221 Fax.No.: 0044 1928 594314	Ciprofloxacine Kabi 100 mg/50 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	100 mg/50 ml
United Kingdom	Fresenius Kabi Limited Cestrian Court, Eastgate Way Manor Park, Runcorn Cheshire WA7 1NT, UK, Tel-No.: 0044 1928 594221 Fax.No.: 0044 1928 594314	Ciprofloxacine Kabi 200 mg/100 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	200 mg/100 ml

United Kingdom	Fresenius Kabi Limited Cestrian Court, Eastgate Way Manor Park, Runcorn Cheshire WA7 1NT, UK, Tel-No.: 0044 1928 594221 Fax.No.: 0044 1928 594314	Ciprofloxacine Kabi 400 mg/200 ml, solution for infusion	2 mg/ml	Solution for infusion	Intravenous use	400 mg/200 ml

ANNEX II

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

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CIPROFLOXACIN KABI 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. Ciprofloxacin exerts a rapid bactericidal effect by inhibiting DNA-gyrase, resulting in inhibition of DNA synthesis. Ciprofloxacin is rapidly and effectively absorbed after oral administration. There is a linear correlation between dose and plasma concentration.

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 need to be adequate.

During the referral procedure the Applicant/Marketing Authorisation Holder was requested to submit:

1. clinical data and discuss the risk/benefit of the proposed dose in urinary tract infections (UTI). The applicant/MAH should discuss both the 100 mg twice daily (bid) dose and the 200 – 400 mg bid dose from a safety and efficacy point of view. In doing so the applicant/ MAH should discuss the data in relation to complicated and uncomplicated, upper and lower urinary tract infections.

2. clinical data and discuss the risk/benefit of the maximum adult daily dose, i.e. whether it should be 400 mg bid or 400 mg three times daily.

The applicant/MAH did not submit any clinical data to address the 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 applicant/MAH performed a review of published clinical studies from the mid 1990's to date, to support the recommended posology of 200-400 mg ciprofloxacin twice daily in the treatment of complicated urinary tract infections. In the majority of studies a regimen of 500 mg b.i.d. p.o. was used. As ciprofloxacin is 70–85% bioavailable, the oral doses of 250-500mg bid. used in most of the published studies presented are equivalent to the 200-400mg b.id. intravenous dose. Other studies comparing efficacy of low and higher dose ciprofloxacin showed superiority of the higher dose both in short term (1, 2) and long term efficacy (2). Two studies of oral doses of 100 mg b.i.d. demonstrated clinical efficacy of 93% and bacterial eradication of 89%, but this was for the treatment of uncomplicated UTI (3) and efficacy of 91% (n=23) without development of resistance (2). No clinical study using 100 mg i.v. twice daily for the treatment of complicated urinary tract infections was identified.

An additional factor for consideration is the emergence of increasing ciprofloxacin resistance, particularly in the last 10-15 years. The applicant has submitted evidence demonstrating the historical development of ciprofloxacin resistance and the decreasing margin between antibiotic resistance and the MIC. Evidence is mounting that suggests a link between inappropriate fluoroquinolone use, development of antimicrobial resistance against the entire fluoroquinolone class, and clinical failure. To maintain the activity of the fluoroquinolone class, clinicians need to implement an evidence-based approach to antimicrobial selection, particularly a strategy in which the most pharmacodynamically potent fluoroquinolone is matched, on an empiric basis when required, to anticipated bacterial pathogens.

Since under-dosing is one of the 3 major factors in the development if antibiotic resistance to fluoroquinolones (4), this may be a case for using the higher dose of ciprofloxacin proposed by the applicant in the treatment of complicated UTIs.

Medical practice in the treatment of complicated UTI's with ciprofloxacin has developed and changed since the time of first licensing in 1987 and the proposed dosing is in line with current medical practice (5) and supported by the published literature.

With respect to the maximal dose, the applicant reviewed 6 clinical studies addressing the safety and efficacy of the proposed high dose ciprofloxacin treatment regimens in critically ill patients. No data was presented comparing the efficacy, safety or prevention of bacterial resistance using the 800mg maximum IV dose licensed in the UK and the 1200mg IV ciprofloxacin proposed by the applicant. No clinical studies in the treatment of complicated or life-threatening urinary tract infections with the high 1200mg [or 1500 mg peroral] maximum dose proposed, were included or reviewed.

However the published data presented demonstrated the safety and efficacy of high-dose ciprofloxacin (daily dose of 1200 mg IV [or 1500 mg peroral]) with or without an option to oral switch, in various serious and life threatening infections. The conditions studied were severe pneumonia, neutropenia, acute bacterial exacerbations of chronic bronchitis, complicated, community-acquired skin and skin structure infections, infections in cancer patients and bacteraemia,. The treatment was well tolerated, the most commonly occurring adverse event were gastrointestinal disorders. The frequencies of probably and/or possibly drug-related adverse events did not differ significantly between ciprofloxacin-treated patients and the comparator groups.

These recommendations are also in line with current treatment guidelines, with clinical practice in most European countries and with the recommendations of previously approved European original and generic ciprofloxacin products. The daily dose of 1200 mg should not however be exceeded.

References (not all submitted are listed)

1.Frankenschmidt A., Naber K.G., Bischoff W., Kullmann K. Once-Daily Fleroxacin Versus Twice-Daily Ciprofloxacin in the Treatment of Complicated Urinary Tract InfectionsJ Urol 1997; 158: 1494-1499.
2. Prat V, Horcickova M, Matousovic K, Hatala M. Comparison of three dosage regimens of ciprofloxacin in urinary tract infections. Int Urol Nephrol. 1990;22(3):201-7.
3. Richard G.A., Mathew C. P., Kirstein J.M., Orchard D.M., Yang J.Y.
Single-Dose Fluoroquinolone Therapy of Acute Uncomplicated Urinary Tract Infection in Women: Results from a Randomized, Double-Blind, Multicenter Trial Comparing Single-Dose to 3-Day Fluoroquinolone Regimens Urology 2002; 59: 334-339
4. Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. Emerg Infect Dis. 2003 Jan;9(1):1-9.
5.Naber KG, Bergman B, Bishop MC, Bjerklund-Johansen TE, Botto H, Lobel B, Jinenez, Cruz F, Selvaggi FP; Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). EAU guidelines for the management of urinary and male genital tract infections. Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). Eur Urol. 2001 Nov;40(5):576-88.

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

Whereas

- The body of published literature and resistance data presented provide adequate justification, both from an efficacy and safety viewpoint, for the dosing regimen of 200-400 mg ciprofloxacin twice daily for the treatment of complicated UTI.

- From the published data, which have demonstrated for the proposed maximum dose 400 mg i.v. 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.

- The applicant submitted in addition to the proposed Summary of Product Characteristics, a proposal for harmonised labelling and package leaflet.

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

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 100 mg/50 ml, solution for infusion
Ciprofloxacin Kabi and associated names (See Annex I) 200 mg/100 ml, solution for infusion
Ciprofloxacin Kabi and associated names (See Annex I) 400 mg/200 ml, solution for infusion

[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

[Each bag with 50 ml contains 100 mg ciprofloxacin.
Each bag with 100 ml contains 200 mg ciprofloxacin.
Each bag with 200 ml contains 400 mg ciprofloxacin.]

Excipient: sodium

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear, colourless solution
pH of the solution: 4.0 to 4.9

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin Kabi 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 Kabi 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 Kabi may also be administered in the treatment of acute lower respiratory tract infections caused by *Pseudomonas aeruginosa* in children and adolescents 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

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. 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.

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 (5-17years) 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.

4.3 Contraindications

Ciprofloxacin Kabi is contraindicated in*:*
- patients with a hypersensitivity to ciprofloxacin, chinolin 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

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.

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 Kabi. In patients with epilepsy or other lesions of the central nervous system (e.g. reduced convulsion threshold, a history of epileptic seizures, diminished cerebral bloodflow, 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 Mycobacerium tuberculosis, false-negative cultures may occur when the specimens are obtained during ciprofloxacin treatment.

Ciprofloxacin Kabi contains 15.1 mmol (347 mg) sodium per 100 ml 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.

Cylosporine
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.

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. Since the risks for humans are unknown Ciprofloxacin Kabi 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 Kabi 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 reactions involve the gastro-intestinal tract and the central nervous system.
The following adverse reactions have been observed:

In this section undesirable effects are defined as follows:

very common	(>1/10)
common	(>1/100,<1/10)
uncommon	(>1/1000,<1/100)
rare	(>1/10 000,<1/1000)
very rare, including isolated reports	(<1/10 000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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.

Nervous system disorders:
Common: perverted sensation of taste, 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.

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.
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.
Very rare: erythema nodosum, erythema multiforme (minor), Stevens-Johnson syndrome, epidermal necrolysis (Lyell Syndrome).

Musculoskeletal, conective tissue and bone 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), aggravation of the symptoms of myasthenia.

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.

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: Quinolone antibacterials (ATC code: J01MA02)

Mode of action:

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. 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.

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;
- Neisseria gonorrhoeae: ≤0.03 µg/ml for susceptible, >0.06 µg/ml for resistant;
- N. meningitides: ≤0.03 µg/ml for susceptible, >0.06 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-positive species
Bacillus anthracis
Gram-negative aerobe species
Citrobacter spp.
Citrobacter freundii
Enterobacter cloacae
Haemophilus influenzae
Moraxella spp.
Moraxella catarrhalis
Morganella spp.
Morganella morganii
Proteus spp.
Proteus mirabilis

Proteus vulgaris
Salmonella spp.
Serratia liquefaciens
Serratia marcescens
Shigella spp.
Shigella flexneri
Shigella sonnei
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.
Streptococcus agalactiae
Streptococcus pneumoniae
S. pneumoniae PEN-R
Streptococcus pyogenes
Gram-negative aerobes
Acinetobacter spp.
Acinetobacter baumannii
Campylobacter spp.
Campylobacter jejuni
Enterobacter spp.
Enterobacter aerogenes
Enterobacter spp. Amp-C producing
Escherichia coli
E. coli ESBL producing
Klebsiella pneumoniae
Klebsiella oxytoca
Klebsiella pneumoniae ESBL producing
Neisseria gonorrhoeae
Pseudomonas aeruginosa
Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecium
Staphylococcus epidermidis
Staphylococcus haemolyticus
Gram-negative aerobes
E. coli multi-resistant
Providencia spp.
Stenotrophomonas maltophilia
Other pathogens
Ureaplasma urealyticum
Anaerobes
Bacteroides fragilis

** 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

Other information:
A study on Rhesus-monkeys that were exposed to anthrax by inhalation revealed that 8/9 animals survived the experiment when these animals were treated from 1 day after anthrax exposure with ciprofloxacin twice daily for a period of 30 days. The MIC of the Bacillus anthrax strain that was applied in this study was 0.08 µg/ml. Because the MIC_{90} for ciprofloxacin of 70 other Bacillus anthrax strains varied between 0.03-0.06 µg/ml, it seems likely that ciprofloxacin would also be effective in other strains than the one that was applied in this study. There are however no sufficient clinical data available to draw conclusion about the effectiveness of ciprofloxacin in the treatment of anthrax in humans. Physicians are recommended to follow current national and/or international consensus documents regarding the treatment of anthrax.

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 administration. 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

Sodium chloride
Sulphuric acid
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

Ciprofloxacin Kabi 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

18 months
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

6.5 Nature and contents of container

Clear flexible polyolefine bag with aluminium overpouch.

[Ciprofloxacin Kabi 100 mg/50 ml solution for infusion: pack sizes: 1, 5, 10, 20, 30 or 40 bags.
Ciprofloxacin Kabi 200 mg/100 ml solution for infusion: pack sizes: 1, 5, 10, 20, 30 or 40 bags.
Ciprofloxacin Kabi 400 mg/200 ml solution for infusion: pack sizes: 1, 5, 10, 20, 30 or 40 bags.]

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Use only clear solutions and undamaged containers.
For single use only. Any unused solution and the bag should be adequately disposed of, in accordance with local requirements.
To be used immediately after the bag is opened.
Do not prepare admixtures in glass bottles.

Ciprofloxacin Kabi 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 s olution with 2.25 mg/ml (0.225 %) or 4.5 mg/ml (0.45 %) sodium chloride solution. Compatibility with these solutions has been proven in the dilution range of 1+1 and 1+4, corresponding to ciprofloxacin concentrations of 0.4 to 1 mg/ml. Unless compatibility is proven, the solution for infusion should always be administered separately (see also section 6.2).
The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colourless.

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 100 mg/50 ml solution for infusion
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

Each bag with 50 ml contains 100 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Sodium chloride, sulphuric acid, sodium hydroxide, water for injections

Contains sodium compounds. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1, 5, 10, 20, 30, 40 x 50 ml

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

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch (number)

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 200 mg/100 ml solution for infusion
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

Each bag with 100 ml contains 200 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Sodium chloride, sulphuric acid, sodium hydroxide, water for injections

Contains sodium compounds. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1, 5, 10, 20, 30, 40 x 100 ml

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

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch (number)

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 400 mg/200 ml solution for infusion
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

Each bag with 200 ml contains 400 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Sodium chloride, sulphuric acid, sodium hydroxide, water for injections

Contains sodium compounds. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1, 5, 10, 20, 30, 40 x 200 ml

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

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch (number)

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKING

Bag

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 100 mg/50 ml solution for infusion
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

Each bag with 50 ml contains 100 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Sodium chloride, sulphuric acid, sodium hydroxide, water for injections

Contains sodium compounds. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
50 ml

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

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch (number)

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKING

Bag

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 200 mg/100 ml solution for infusion
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

Each bag with 100 ml contains 200 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Sodium chloride, sulphuric acid, sodium hydroxide, water for injections

Contains sodium compounds. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
100 ml

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

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch (number)

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKING

Bag

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Kabi and associated names (See Annex I) 400 mg/200 ml solution for infusion
[See Annex I – To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for infusion contains 2 mg ciprofloxacin (as hydrogen sulphate)

Each bag with 200 ml contains 400 mg ciprofloxacin.

3. LIST OF EXCIPIENTS

Sodium chloride, sulphuric acid, sodium hydroxide, water for injections

Contains sodium compounds. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
200 ml

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

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep infusion bag in the overpouch until ready to use in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch (number)

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ciprofloxacin Kabi and associated names (See Annex I) 100 mg/50 ml, solution for infusion
Ciprofloxacin Kabi and associated names (See Annex I) 200 mg/100 ml, solution for infusion
Ciprofloxacin Kabi and associated names (See Annex I) 400 mg/200 ml, solution for infusion

[See Annex I – To be completed nationally]

Ciprofloxacin (as hydrogen sulphate)

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 KABI IS AND WHAT IT IS USED FOR

Ciprofloxacin Kabi is an antibiotic.

Ciprofloxacin Kabi 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 Kabi:
- complicated urinary tract infections
- certain lower respiratory tract infections including pneumonia
- complicated skin and soft tissue infections
- bone infections.

Children and Adolescents
Ciprofloxacin Kabi 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 KABI

You must NOT be given Ciprofloxacin Kabi in the following cases:
- known allergic reaction to ciprofloxacin or any of the other ingredients of Ciprofloxacin Kabi or other medicines of the quinolone type
- children aged below 5 years
- 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

- patients with a history of tendon disorder related to fluoroquinolone administration
- you are pregnant or wish to become pregnant
- you are breast-feeding.

Take special care with Ciprofloxacin Kabi
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 suffers 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.
- 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 Kabi. 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 Kabi as the result of this test may be false.

Using other medicines
If Ciprofloxacin Kabi 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.

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 Kabi 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
You must not be given Ciprofloxacin Kabi 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.

Breast-feeding
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 Kabi 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 Kabi
If you are on a low-sodium diet, take into account that 100 ml of Ciprofloxacin Kabi contain 15.1 mmol (= 347 mg) sodium.

3. HOW TO USE CIPROFLOXACIN KABI

Dosage
The Ciprofloxacin Kabi 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 thrice 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 of administration
Ciprofloxacin Kabi should be administered via a short-term intravenous infusion (infusion into a vein) over 60 minutes.

Duration of treatment
The duration of treatment with Ciprofloxacin Kabi 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 Kabi 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 Kabi- 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

Infections and infestations
Uncommon: fungal infection (moniliasis)

Blood and lymphatic system disorders
Uncommon: increase in eosinophilic cells (eosinophilia), reduction in white blood cells (leucopenia) which makes infections more likely
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)
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)

Immune system disorders
Rare: 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)
Very rare: 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)

Metabolism and nutrition disorders
Rare: increased blood sugar level (hyperglycaemia)

Mental (psychiatric) disorders
Rare: anxieties, nightmares, severe depression, seeing things or hearing voices that do not exist (hallucinations)
Very rare: disturbed control of own behaviour and actions (psychotic reactions)

Nervous system disorders
Common: distorted sensation of taste, dizziness, headache, difficulty in sleeping (insomnia), restlessness (agitation), confusion
Rare: reduced taste, altered sensation (paraesthesia), shaking (tremor), spasms/ convulsions (seizures), severe headache (migraine)
Very rare: 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)

Eye disorders
Rare: altered vision such as double vision (diplopia) and seeing all objects in a certain colour (chromatopsia)

Ear and inner ear disorders
Rare: ringing in the ear (tinnitus), transient hearing loss (particularly high frequencies)

Heart disorders
Rare: increased heart rate (tachycardia)
Very rare: 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.

Blood vessel disorders

Uncommon: inflammation of a vein related to a blood clot (thrombophlebitis); the vein is often sensed as a tender hard strand covered with red skin
Rare: fainting (syncope), widening of blood vessel (vasodilation)
Very rare: 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)

Breathing and chest disorders
Rare: shortness of breath (dyspnoea), swelling of the voice box (larynx) with difficulties in breathing (larynx oedema)

Disorders of the stomach and intestine
Common: nausea, diarrhoea
Uncommon: vomiting, digestive disorders, gassiness (flatulence), loss of appetite, abdominal pain
Rare: 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)
Very rare: fungal infection in the gastrointestinal system (gastrointestinal moniliasis), pancreas inflammation (pancreatitis)

Disorders of the liver and gall-bladder
Rare: 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)
Very rare: liver inflammation (hepatitis), destruction of liver tissue (liver cell necrosis, very rarely resulting in life-threatening liver failure)

Disorders of the skin and connective tissue
Common: rash
Uncommon: itching (pruritus), spot-shaped rash (maculopapular rash), hives (urticaria)
Rare: increased sensitivity to light (photosensitivity)
Very rare: 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)

Disorders of the skeletal muscles, tendons and bones
Uncommon: joint pain (arthralgia)
Rare: muscular pain (myalgia), joint disorder (swollen joints)
Very rare: 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)

Disorders of the kidney and urinary tract
Rare: 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)

General disorders and administration site conditions
Uncommon: general sensation of weakness, fatigue (asthenia), irritation or pain at the injection site
Rare: perspiration

Investigations

Uncommon: 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)
Very rare: increased blood level of amylase (enzyme that breaks down starch) and lipase (enzyme that breaks down fats).

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 KABI

Keep out of the reach and sight of children.

Do not use Ciprofloxacin Kabi 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.
- Store the infusion bag in the overpouch until it is used in order to protect from light.

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

6. FURTHER INFORMATION

What Ciprofloxacin Kabi contains
- The active substance is ciprofloxacin (as hydrogen sulphate).
  Each bag of 50 ml contains 100 mg of ciprofloxacin. Each bag of 100 ml contains 200 mg of ciprofloxacin. Each bag of 200 ml contains 400 mg of ciprofloxacin.
- The other ingredients are sodium chloride, sulphuric acid, sodium hydroxide for pH adjustment, water for injections

What Ciprofloxacin Kabi looks like and contents of the pack
Ciprofloxacin Kabi is a sterile, clear and colourless solution.
It is contained in a clear flexible polyolefine bag with aluminium overpouch containing 50 ml solution.
It is contained in a clear flexible polyolefine bag with aluminium overpouch containing 100 ml solution.
It is contained in a clear flexible polyolefine bag with aluminium overpouch containing 200 ml solution.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[See Annex I – To be completed nationally]

Manufacturer:
Fresenius Kabi Norge AS
Postboks 430
N-1753 Halden
Norway

This medicinal product is authorised in the Member States of the EEA under following names:

[See Annex I – To be completed nationally]

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

[To be completed nationally]

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

Use only clear solutions and undamaged containers.

For single use only. Any unused solution and the bag should be adequately disposed of, in accordance with local requirements.
To be used immediately after the bag is opened.
Do not prepare admixtures in glass bottles.

Ciprofloxacin Kabi 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. Compatibility with these solutions has been proven in the dilution range of 1+1 and 1+4, corresponding to ciprofloxacin concentrations of 0.4 to 1 mg/ml. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. 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 and colourless.