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
United Kingdom	Nycomed Danmark ApS Langebjerg 1 DK-4000 Roskilde Denmark		Ciprofloxacin	2 mg/ml	Solution for infusion	Intravenous use	50 ml, 100 ml, 200 ml
Denmark		Nycomed Danmark ApS Langebjerg 1 DK-4000 Roskilde Denmark	Ciprofloxacin Nycomed	2 mg/ml	Solution for infusion	Intravenous use	50 ml, 100 ml, 200 ml
Finland		Nycomed Danmark ApS Langebjerg 1 DK-4000 Roskilde Denmark	Ciprofloxacin Nycomed	2 mg/ml	Solution for infusion	Intravenous use	50 ml, 100 ml, 200 ml
Norway		Nycomed Pharma AS Drammernsveien 852 NO-1372 Asker Norway	Ciprofloxacin Nycomed	2 mg/ml	Solution for infusion	Intravenous use	50 ml, 100 ml, 200 ml
Sweden		Nycomed AB Tegeluddvägen 17-21 S-102 53 Stockholm Sweden	Ciprofloxacin Nycomed	2 mg/ml	Solution for infusion	Intravenous use	50 ml, 100 ml, 200 ml

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE PRODUCT INFORMATION

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF Ciprofloxacin Nycomed 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 be adequate.

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

1. submit 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. submit 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).

To support the recommended posology of 200-400 mg ciprofloxacin twice daily in the treatment of complicated urinary tract infections, the applicant/MAH provided substantial scientific evidence. A large number of published studies have demonstrated the efficacy and safety of ciprofloxacin, using the intravenous dose 200-400 mg twice daily and the corresponding oral dosage 250-500 mg bid in the treatment of urinary tract infections. Further literature searches showed that only a minority of the published literature mention the use of 100 mg intravenous ciprofloxacin twice daily, e.g. Martindale indicates that the usual adult intravenous dose is 100 mg to 400 mg twice daily, but the dosages is not related specifically to treatment of urinary tract infections. No clinical study using 100 mg intravenous twice daily for the treatment of complicated urinary tract infections, was identified.

Medical practice in the treatment of UTI's with ciprofloxacin has changed and developed since the time of first licensing in 1987. The recommended posology of 200-400 mg ciprofloxacin twice daily is in line with current medical practice, supported by the published literature presented from the mid 1990's to date.

In addition a dose-dependent clinical response of fluoroquinolones in the treatment of complicated UTI has been demonstrated in a clinical trial by Frankenschmidt et al (1). According to pharmacodynamic studies, ciprofloxacin, like other fluoroquinolones, exhibits concentration dependent killing. Thus AUC over MIC is determinative for efficacy and it is therefore crucial that substantial concentrations are achieved at the site of the target pathogens. The antimicrobial activity of fluoroquinolones in urine is reduced depending on pH and various solubles, mainly cations. In addition, in complicated UTI, biofilm formation may play an important role where susceptibility of the pathogens is several folds reduced compared with planctonic or pure culture cells. Naber et al (2) determined the *ex vivo* urinary bactericidal titres (UBT) of various fluoroquinolones and concluded that for a highly susceptible strain of *E. coli* a low dose of ciprofloxacin e.g. 100 mg bid, may be

sufficient for the treatment of uncomplicated UTI, while for the treatment of complicated UTI due to *Pseudomonas aeruginosa* at least a dose of 500 mg bid of ciprofloxacin is needed (equivalent to 400 mg intravenous twice daily).

It has been shown that exposure to quinolones at subinhibitory concentrations significantly increase the mutation rate in *E. coli*, staphylococci, pneumococci and *Mycobacterium* spp., as well as selecting for resistance *per se* (3). The importance of using dosage regimens of fluoroquinolones leading to *in vivo* concentrations exceeding the mutant prevention concentrations, thus avoiding first-step mutants, is currently stressed by leading experts within the field.
An adequate dosing, in order to achieve optimal clinical efficacy and to prevent emergence of antimicrobial resistance, is therefore crucial both for the individual patient and for the society, especially in light of the current increase of resistant uropathogens.

To support the proposed maximum dose of 1200 mg (400 mg three times daily) instead of 800 mg, the applicant/MAH referred to the published literature.

No clinical studies in the treatment of complicated or life-threatening urinary tract infections with the high 1200 mg intravenous [or 1500 mg peroral] maximum dose proposed, were included or reviewed. However the published data presented demonstrated the safety and efficacy of thus high-dose ciprofloxacin (daily dose of with or without an option to oral switch, in various serious and life threatening infections (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.

In light of the increasing rate of quinolone resistance in urinary pathogens in Europe, an optimal dosage regimen is therefore considered important, because underdosing may lead to an impaired clinical response and pose a risk for emergence of resistant strains. Resistance development is beside absolute quantitative use of quinolone agents also driven by pharmacokinetic and pharmacodynamic (PK/PD) factors. Current PK/PD data stress the importance of adequate dosing in order to circumscribe emergence of resistance.

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. 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.
3. Marcusson LL et al. Mutant prevention concentrations of ciprofloxacin for urinary tract infection isolates of Escherichia coli. 2001; J. Antimicrob. Chemother. 2005; 55:938-943.

GROUNDS FOR AMENDMENT OF THE PRODUCT INFORMATION

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.

- 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.

The CHMP has recommended the granting of the Marketing Authorisation(s), as well as the text to be included in the Summary of Product Characteristics, Package Leaflet and Labelling. These are set out in Annex III for Ciprofloxacin Nycomed and associated names (see Annex I).

ANNEX III

AMENDMENTS TO SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET AND LABELLING

SUMMARY OF PRODUCT CHARACTERISTICS

The following text shall be included in the Summary of Product Characteristics:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Children and adolescents
Acute pulmonary exacerbation of cystic fibrosis in children and adolescents (5-17 years) caused by *Pseudomonas aeruginosa.*
Ciprofloxacin Nycomed is not indicated for other infections in this age group.

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

4.2 Posology and method of administration

The dosage of intravenous ciprofloxacin is determined by the severity and type of infection, the sensitivity of the causative organism(s) and the age, weight and renal function of the patient.
The recommended dosage range for adults in different types of infection is given in the table below. The usual dosage range for adults is 200-400mg twice daily. In very serious or life threatening infections, the dosage can be increased to 400 mg three times daily. The product may be infused directly and administered by short-term infusion over periods of 30-60 minutes. The 400mg dose should be administered over a period of 60 minutes. Initial intravenous administration may be followed by oral treatment. The product should not be mixed with other drug products that are chemically or physically unstable at its pH of 3.9-4.5 (see section 6.2). However, Ciprofloxacin 2mg/ml Solution for Infusion has been shown to be compatible with Ringer's solution, 0.9% sodium chloride solution, 5% and 10% glucose solutions, glucose/saline and fructose 10% solution. Unless compatibility is proven, the infusion solution should always be administered separately. In addition, discard any unused portion of product immediately after use.

Adults
The following dosages for specific types of infection are recommended:

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

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

Impaired Renal function
The following dose adjustments are recommended:

Creatinine clearance ml/min	**Recommended dose adjustment**
31-60 creatinine clearance (serum creatinine 120-170 µmol/l)	Maximum daily dose intravenous 800 mg, divided in two doses
≤ 30 creatinine clearance (serum creatinine > 175 µmol/l)	Maximum daily dose intravenous, 400 mg*

*Patients in haemodialysis: On the day of dialysis the dose of Ciprofloxacin Nycomed should be given intravenously after dialysis.

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

Impaired hepatic function
No adjustment of dosage is necessary.

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

Adolescents and children
Ciprofloxacin Nycomed is not recommended for use in children below 18 years of age.
As with other medicinal products in its class, ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals.

However analysis of available safety data from ciprofloxacin used in patients below 18 years for which the majority had cystic fibrosis, did not disclose any evidence of drug related cartilage or articular damage,.
Clinical and pharmacokinetic data support the use of ciprofloxacin in paediatric cystic fibrosis patients (aged 5-17 years) with acute pulmonary exacerbation associated with *P. aeruginosa* infection, at a dose of 10mg/kg intravenous three times daily (maximum daily dose 1200mg), see section 4.4 and 5.2.
The infusion should be administered over 60 minutes.

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON {50 ml vial, 100 ml and 200 ml vial}

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Nycomed 2mg/ml solution for infusion
[See Annex I - To be completed nationally]
Ciprofloxacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml: Ciprofloxacin lactate corresponding to 2 mg of ciprofloxacin

3. LIST OF EXCIPIENTS

Excipents: Hydrochloric acid, lactic acid, sodium chloride, water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for Infusion
50 ml vial
100 ml vial
200 ml vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenoususe.

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

Do not use if crystals are present.

8. EXPIRY DATE

EXP.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.
Keep the vial in the outer carton 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

Discard any unused portion of the product immediately after use.

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

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL {50 ml vial, 100 ml vial and 200 ml vial}

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

Ciprofloxacin Nycomed 2mg/ml Solution for Infusion
[See Annex I - To be completed nationally]

intravenous

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 ml
100 ml
200 ml

6. OTHER

PACKAGE LEAFLET

The following text shall be included in the Package Leaflet:

1. WHAT CIPROFLOXACIN IS AND WHAT IT IS USED FOR

Ciprofloxacin is an antibiotic agent belonging to the group called quinolones. It acts by killing bacteria that can cause infections.

Ciprofloxacin Nycomed is used for the treatment of several types of infections in adults such as pneumonia, certain types of urinary tract infections, infections in the prostate, infections in the abdomen and around the gut, certain skin infections, infections in the bones and of infections in patients with poor immune system.

In children and teenagers (age 5-17) who have cystic fibrosis, Ciprofloxacin Nycomed may also be used for treating certain types of lung infections.

3. HOW TO USE CIPROFLOXACIN

Ciprofloxacin Nycomed will be administered by your doctor or a specialist.
The dose and the duration of the treatment are depending upon the severity and type of your infection. However it is important that you are given a complete course of the treatment, even if you begin to feel better after a few days, otherwise your symptoms may return.

Adults
Complicated urinary tract infections, Respiratory tract infections, Pneumonia and other infections
200 – 400 mg twice daily.

The maximum daily dose in very serious or life-threatening infections can be up to 1200 mg daily, administered as 400 mg three times daily

Adolescents and Children (age 5 – 17 years)
Acute pulmonary exacerbation in paediatric cystic fibrosis patients:
10 mg/kg three times daily (maximum 1200 mg daily), or 10 mg/kg intravenous three times daily (maximum 1200 mg daily) followed by 20 mg/kg orally twice daily (maximum 1500 mg daily)

Duration of treatment
Adults
The usual duration of treatment is between 5 -7 days, but it may be longer if your infection is more persistent or severe.

Children and adolescent (aged 5 – 17 years):
The duration of treatment for certain lung infections in children and adolescents with cystic fibrosis is 10 – 14 days.