CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ciprinol 250, 500, and 750 mg film-coated tablets
Krka Pharma Dublin Ltd., Ireland

ciprofloxacin hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/857/001-003/MR
Registration number in the Netherlands: RVG 32444-6

14 August 2009

Pharmacotherapeutic group:	antibacterial quinolone derivate
ATC code:	J01MA02
Route of administration:	oral
Therapeutic indication:	*Adults:* infections of upper and lower urinary tract, respiratory tract, or genital organs. Severe bacterial enteritis. Severe skin and soft tissue infections and osteomyelitis caused by gram-negative bacteria. Severe systemic infections caused by Gram-negative bacteria. *Children and adolescents:* Acute pulmonary exacerbation of cystic fibrosis in children and adolescents (5-17 years) caused by Pseudomonas aeruginosa.
Prescription status:	prescription only
Date of first authorisation in NL:	18 May 2005
Concerned Member States:	Mutual recognition procedure with AT, DE, DK, FI, IT, and SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ciprinol 250, 500, and 750 mg film-coated tablets, from Krka Pharma Dublin Ltd. The date of authorisation was on 18 May 2005 in the Netherlands. The product is indicated for treatment of infections caused by ciprofloxacin-sensitive pathogens, such as:

Infections of:
- The respiratory tract. Ciprofloxacin may be indicated for treating pneumonia due to gram-negative pathogens. In pneumococcal pneumonia ciprofloxacin is not the drug of first choice.
- The urinary tract: acute uncomplicated cystitis, complicated infections and pyelonephritis.
- The genital organs: acute, uncomplicated gonorrhoea, prostatitis.
- Severe bacterial enteritis.
- Severe skin and soft tissue infections caused by Gram-negative bacteria.
- Osteomyelitis caused by Gram-negative bacteria.
- Severe systemic infections caused by Gram-negative bacteria: e.g. septicaemia, peritonitis (in case of peritonitis, the anaerobic component should be covered by an anti-anaerobe agent).
- Infections in immuno-suppressed patients.

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

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

A comprehensive description of the indications and posology is given in the SPC.

Ciprofloxacin is a synthetic 4-quinolone derivative antibacterial agent of the fluoroquinolone class. As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and tapoisomerase IV.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Ciproxin 250, 500 and 750 mg tablets (NL License RVG 12241-3) which have been registered in the Netherlands by Bayer since 1988 (original product). In addition, reference is made to Ciproxin and Ciprobay authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Ciprobay 250, 500 and 750 mg tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

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

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for thes product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of these products prior to granting its national authorisation.

Active substance
The active substance is ciprofloxacin hydrochloride, an established active substance, described in the European Pharmacopoeia (Ph.Eur.*). Ciprofloxacin hydrochloride is a white to pale yellow, odourless, crystalline powder.

Manufacture
The CEP procedure is used for one the active substance manufacturers. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

For a second active substance manufacturer, full documentation is included in the dossier. The charts of the manufacturing processes following two routes, and a detailed description of these processes have been submitted, including structural formulas. The manufacturing process has been adequately described.

Specification
For the first active substance manufacturer, the active substance specification is considered adequate to control the quality and meets the requirements of the specific monographs in the Ph.Eur and CEP. For the second manufacturer, no CEP was submitted. The specifications of another manufacturer also meet the requirements of the specific monographs in the Ph. Eur., with additional specifications for ‘residual solvents’ which conform to in-house specifications. From one active substance supplier, three certificates of analysis are included demonstrating compliance with this specification. From another active substance supplier 3 production scale batches were presented of each synthetic route, also showing compliance with the specification.

Stability
No retest period could be granted to the substance from one active substance supplier. The substance should be tested for compliance with the specification prior to use. The MAH has committed to submit results of both long term and accelerated stability studies performed according to the Guideline on stability testing when available.

For another active substance manufacturer, stability data on the active substance have been provided for 3 batches (stored at 25ºC/60%RH, 30ºC/60%RH, 40ºC/75%RH, 40ºC, and 50ºC) of synthesis route I over 24 months. For synthesis route II, stability data have been provided for 3 batches stored at 25ºC/40%RH, 25ºC/60%RH, 30ºC/60%RH, and 40ºC/75%RH.
There has been no significant change of the tested parameters caused by storage neither at normal nor at accelerated conditions. The photostability test did not show any significant change of the tested parameters. The samples stored at daylight showed a slight raise of the amount of related substances. However, the amount of related substances remained far below the upper specification limit. The other tested parameters did not change significantly.
Based on the data submitted from this supplier, a retest period could be granted of 2 years when stored in original package and protected from light.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Ciprinol 250, 500, and 750 mg film-coated tablets contain as active substance 291 582, and 873 mg of ciprofloxacin hydrochloride respectively, and are white, round (250 mg) or oval (500 and 750 mg), plain on one side with a break-line on the reverse (250 and 500 mg) or with a break-line on both sides (750 mg). Their weight is respectively 415, 790and 1090 mg.

The film-coated tablets are packed in blisters with transparent PVC/PVDC foil and heat sealing aluminium foil.

The excipients are:
Tablet coat: Hypromellose (E464), Talc, Titanium dioxide (E 171), and Propylene glycol.
Tablet core: Croscarmellose sodium, Silica (colloidal anhydrous), Magnesium stearate (E572), Cellulose (microcrystalline (E460 ('i))), Sodium starch glycollate Type A, and Povidone

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The used excipients are well known and safe in the proposed concentrations. All excipients comply with the Ph.Eur. Certificates of analysis were included. The amounts of excipients are not proportional when comparing the various tablet strengths. It should however be noted that the MAH performed bioequivalence studies with each strength. The components are comparable to those used in the Dutch reference product Ciproxin.
Critical aspects of the formulation are solubility of the drug substance, water content and particle size. Ciprofloxacine hydrochloride exhibits pseudopolymorphism i.e. the presence of a hydrate form. The monohydrate form of ciprofloxacin hydrochloride is always used for the production of the tablets.

Bioequivalence studies
The in vitro dissolution studies for the bioequivalence batches showed similarity with the dissolution profiles of the reference batches. In addition, the MAH performed dissolution tests with innovator batches from IE, UK, NL, DK, FI and SE. The dissolution conditions were 900 ml 0.01 M HCl, 50 rpm. In all cases more than 90% is dissolved within 15 minutes.

Manufacturing process
The production process is adequately described. Mixing times and sieve measures are indicated. The manufacturing process has been validated according to relevant European/ICH guidelines.
A retrospective process validation was performed regarding two parameters (average weight and dissolution rate) for 15 consecutive batches. The individual values obtained are within the adopted limits and the mean values are close to the target value. Since more than 60% of the film-coated tablets consist of active substance, homogeneity problems were not expected. Absence of data regarding this parameter was therefore acceptable. In addition, the stated specification requirements sufficiently guarantee adequate quality control of the products at issue. It should be noted that at the time of application the note for guidance on Process validation was not adopted yet. This note for guidance was therefore not taken into account in the assessment of the products.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identification, assay, related substances, water content, uniformity of mass, dissolution, hardness, disintegration, and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

The MAH has submitted analysis results of several production scaled batches of 250 mg, 500 mg and 750 mg tablets. Though not always all parameters were investigated, it is clear from all certificates that the MAH is capable of producing batches that comply with the release specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches of 250 mg, 3 batches of 500 mg and 2 batches of 750 mg for 36 months. The storage conditions were 25ºC/60%RH, 30ºC/60%RH and 40ºC/75%RH. Two production scaled batches of 750 mg are deemed sufficient as the composition of the tablets and the observed stability data are comparable.
For all batches the investigated parameters are stable at all test conditions. The tablets show good stability when stored under normal conditions and at increased temperature/humidity. Furthermore, it is evident from the available literature that ciprofloxacin is sensitive to light. The tablets should therefore be appropriately protected from light. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage condition is “store in original package”.
After finalisation of the MRP, the shelf life has been changed from 3 years to 5 years by a type IB variation NL/H/0857/001-003/IB/007 (see ‘Steps taken after the finalisation of the initial procedure’).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. The MAH has included a declaration that magnesium stearate is from vegetable origin in order to guarantee safety regarding TSE.

II.2 Non clinical aspects

This product is a generic formulation of Ciproxin, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ciprofloxacin hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profiles of the test products Ciprinol 250, 500, and 750 mg film-coated tablets are compared with the pharmacokinetic profiles of the German reference products 250, 500 and 750 mg Ciprobay tablets.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Ciprofloxacin hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ciprofloxacin hydrochloride. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioequivalence study 1 (250 mg tablet)

Test: Ciprinol 250 mg film-coated tablet (Krka Pharma Dublin Ltd).
Reference: Ciprobay 250 mg tablet (Bayer, Germany).

A two-way, single-dose, randomised crossover bioequivalence study was carried out under fasted conditions in 28 healthy male volunteers, aged 18 to 35 years. Each subject received a single dose (250 mg) of one of the 2 ciprofloxacin hydrochloride formulations. The tablet was orally administered with 120 ml water after a 10h fasting period. There were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after administration of the products.

One subject withdrew his consent before the start of the study and one subject was excluded because of urticaria on the day before the beginning of the study. Twenty-six subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ciprofloxacin under fasted conditions.

Treatment N=26	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5.3 ± 1.2	5.6 ± 1.3	1.3 ± 0.3	1.0 ± 0.3	4.4 ± 1.1
Reference	5.4 ± 1.4	5.7 ± 1.3	1.4 ± 0.3	1.1 ± 0.5	4.6 ± 1.0
***Ratio (90% CI)**	1.00 (0.92 – 1.07)	---	0.96 (0.87 – 1.06)	---	---
CV (%)	15.9	---	20.5	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ciprofloxacin under fasted conditions, it can be concluded that Ciprinol 250 mg film-coated tablets and Ciprobay 250 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study 2 (500 mg)

Test: Ciprinol 500 mg film-coated tablet (Krka Pharma Dublin Ltd).
Reference: Ciprobay 500 mg tablet (Bayer, Germany).

A two-way, single-dose, randomised crossover bioequivalence study was carried out under fasted conditions in 27 healthy male volunteers, aged 19 to 25 years. Each subject received a single dose (500 mg) of one of the 2 ciprofloxacin hydrochloride formulations. The tablet was orally administered with 120 ml water after a 10h fasting period. There were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after administration of the products.

One subject withdrew because of angina a few days before the start of the study. Twenty-six subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ciprofloxacin under fasted conditions.

Treatment N=26	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	9.7 ± 2.0	10.0 ± 2.0	2.2 ± 0.5	1.2 ± 0.3	4.6 ± 0.6
Reference	9.4 ± 1.8	9.7 ± 1.9	2.2 ± 0.4	1.1 ± 0.4	4.7 ± 0.6
***Ratio (90% CI)**	1.03 (0.96 – 1.11)	---	0.97 (0.89 – 1.07)	---	---
CV (%)	15.5	---	19.7	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ciprofloxacin under fasted conditions, it can be concluded that Ciprinol 500 mg film-coated tablets and Ciprobay 500 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study 3 (750 mg)

Test: Ciprinol 750 mg film-coated tablet (Krka Pharma Dublin Ltd).
Reference: Ciprobay 750 mg tablet (Bayer, Germany).

A two-way, single-dose, randomised crossover bioequivalence study was carried out under fasted conditions in 26 healthy male volunteers, aged 18 to 45 years. Each subject received a single dose (750 mg) of one of the 2 ciprofloxacin hydrochloride formulations. The tablet was orally administered with 200 ml water after a 10h fasting period. There were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after administration of the products.

All subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ciprofloxacin under fasted conditions.

Treatment N=26	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16.1 ± 3.1	16.8 ± 3.2	3.4 ± 0.8	1.3 ± 0.4	4.8 ± 0.4
Reference	16.1 ± 2.7	16.8 ± 2.9	3.2 ± 0.8	1.5 ± 0.5	4.8 ± 0.3
***Ratio (90% CI)**	1.00 (0.92 – 1.09)	---	1.07 (0.96 – 1.18)	---	---
CV (%)	17.9	---	21.6	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ciprofloxacin under fasted conditions, it can be concluded that Ciprinol 750 mg film-coated tablets and Ciprobay 750 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Ciprofloxacin was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ciprofloxacin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the Dutch innovator product Ciproxin marketed by Bayer and with NL/H/315/01-03/E01 and new information, based on the recently revised MRP-SPC's (e.g. DK/H/202, DK/H/204, SE/H/238 and NL/H/305/E01). Furthermore in section 4.5 the interaction with CYP1A2 inhibitors is now mentioned, following the discussions in the Pharmacovigilance Working Party.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. Gender, educational level and age distribution in these rounds is acceptable. Adequate areas for the questionnaire were identified as important for the safe and effective use of Ciprinol tablets.

The pilot test led to changes to the PIL and questionnaire. The amended PIL was then the subject of Round 1. This led to the conclusion that changes in the text and lay-out were needed. A revised PIL was the subject of Round 2.

After the second round, acceptable scores were obtained. At least 80% correct answers to 13 out of 14 questions were obtained and 70% correct answers for 1 out of 14 questions. Results of round 2 suggest that further improvements to the lay-out would be beneficial. The MAH has made some additional changes to the lay-out, but these changes have not been user tested. The RMS agrees with the conclusion that the current version does not require additional testing, based on the results obtained in the second round.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ciprinol 250, 500, and 750 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Ciproxin 250, 500 and 750 mg tablets. Ciproxin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the Dutch innovator product Ciproxin marketed by Bayer and with NL/H/315/01-03/E01 with some small modifications. The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Ciprinol 250, 500 and 750 mg were authorised in the Netherlands on 18 May 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ciprinol 250, 500 and 750 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 25 September 2006.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from September 2006 to September 2009.
However, the MAH is recommended to take part in the EU synchronisation project in which PSURs will be scheduled according to a harmonised birth date for ciprofloxacin, this might change the expected PSUR submission date and covered period.

The date for the first renewal will be: 25 September 2011.

The following post-approval commitment has been made during the procedure:

<u>Quality – medicinal product</u>
- The MAH committed to start a stability study with products manufactured with granulate and uncoated tablets at the end of the holding times.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in pack size of the finished product. Change in the number of units in a pack. Change outside the range of the currently approved pack sizes. Addition of cartons with 6 (500 mg).	NL/H/0857/ 002/IB/001	IB	7-12-2006	6-1-2007	Approval	N
Change in pack size of the finished product. Change in the number of units in a pack. Change within the range of the currently approved pack size. Addition carton 12 (750 mg).	NL/H/0857/ 003/IA/002	IA	7-12-2006	21-12-2006	Approval	N
Change in pack size of the finished product. Change in the number of units in a pack. Change within the range of the currently approved pack size. Addition of pack size of 16. Update SPC (part 6.5) and PIL.	NL/H/0857/ 002/IA/003	IA	19-9-2007	3-10-2007	Approval	N
Change in the name and/or adress of the marketing authorization holder. Teva Pharma Italia S.r.l. Viale G Richard 7-20143 Milano Italy changes into: Teva Italia S.r.l. Via Messina 38 20154 Milano Italy.	NL/H/0857/ 001-003/IA/ 005	IA	20-5-2008	3-6-2008	Approval	N
Change in the name and/or adress of the marketing authorization holder. Change in the name of the authorisation holder in AT and DE.	NL/H/0857/ 001-003/IA/ 006	IA	4-6-2008	18-6-2008	Approval	N
Change in the shelf-life of the finished product as packaged for sale. Extension of the shelf-life from 36 to 60 months.	NL/H/0857/ 001-003/IB/ 007	IB	17-2-2009	19-3-2009	Approval	N