C B G
M E B

PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Ciprofloxacin-hameln 2 mg/ml, solution for infusion
hameln pharma plus gmbh, Germany

ciprofloxacin

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/1484/001/DC
Registration number in the Netherlands: RVG 103365

16 June 2010

Pharmacotherapeutic group:	quinolone antibacterials; fluoroquinolones
ATC code:	J01MA02
Route of administration:	intravenous
Therapeutic indication:	infections (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	20 April 2010
Concerned Member States:	Decentralised procedure with DE, DK, FI, NO, UK
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 Ciprofloxacin-hameln 2 mg/ml, solution for infusion, from Hameln Pharma Plus GmbH. The date of authorisation was on 20 April 2010 in the Netherlands.

The product is indicated for the treatment of the following infections:

Adults

- Lower respiratory tract infections due to Gram-negative bacteria
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to Neisseria gonorrhoeae
- Pelvic inflammatory disease including cases due to Neisseria gonorrhoeae
  In the above genital tract infections when thought or known to be due to Neisseria gonorrhoeae it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.
- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

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

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination. Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ciproxin 100 mg/50 ml, 200 mg/100 ml and 400 mg/200 ml, solution for infusion (NL License RVG 12245, 12246 and 17111) which have been registered in the Netherlands by Bayer B.V. since 15 August 1988 (100 mg/50 ml, 200 mg/100 ml) and 8 August 1994 (400 mg/200 ml). In addition, reference is made to Ciproxin authorisations in the individual member states (reference product).

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

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

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. As Ciprofloxacin-hameln 2 mg/ml, solution for infusion is a product for parenteral use in aqueous solution, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

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 this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ciprofloxacin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Ciprofloxacin is a slightly yellow crystalline powder, insoluble in water and very slightly soluble in ethanol and dichloromethane. It is soluble in diluted acetic acid.

The CEP procedure is used for both suppliers of the active substance. 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.

Manufacturing process
The CEPs adequately cover the drug substance specifications for both drug substance manufacturers. Batch analytical data have been provided on 3 batches from each manufacturer, demonstrating compliance with the specifications.

Stability of drug substance
For one supplier, stability data on the product has been provided on three full-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% (6 months). The stability batches were adequately stored. No changes were observed at both conditions. The proposed retest period of 5 years could therefore be granted.
The active substance from the other manufacturer is stable for 5 years when stored under the proposed conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Ciprofloxacin-hameln 2 mg/ml contains as active substance contains as active substance 2.5 mg ciprofloxacin lactate per ml, equivalent to 2 mg ciprofloxacin.
The product is a clear, colourless or slightly yellow, sterile aqueous solution with pH 3.9-4.5.

The solution for infusion is packed in 50 ml, 100 ml and 200 ml colourless glass infusion vials (hydrolytic class II) with a bromobutyl rubber stopper with aluminium flip-off cap.

The excipients are: lactic acid, sodium chloride, hydrochloric acid (for pH adjustment), water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The exipients used are the same as the ones in the innovator product. Essential similarity with the innovator's product has been proven. The main development studies consisted of compatibility testing with different commonly used solutions for infusion. The drug product was shown to be stable for 24 hours when mixed with NaCl 0.9 %, Ringer solution (also with sodium lactate), glucose 5 and 10 %, fructose 10 %, glucose/saline solution and Hartmann's solution if the mixture is protected from direct sunlight. The pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process consists of several dissolution steps, after which the pH is adjusted. The solution is then filtered and filled in vials. The filled vials are sterilized by autoclaving. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full-scale batches.

Microbiological attributes

The drug product is sterilised in its final packaging by means of moist heat. Microbiological evaluation is performed on the finished drug product according to the current Ph.Eur. monograph.

Control of excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for clarity, color, visible particles, extractable volume, pH value, identity, content of ciprofloxacin, lactic acid and sodium chloride, related substances, sterility and bacterial endotoxins. Except for the limit for single unknown impurities, all release and shelf life requirements are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full scale batches stored at 25°C/60% RH (18 months) and 40°C/75% (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Ph.Eur. type II glass vials closed with a bromobutyl rubber stopper. No changes or trends are observed at both storage conditions. In a photostability study the drug product was shown to be unstable to light exposure. The claimed shelf life of 30 months could be granted, with the storage requirement *Do not refrigerate or freeze. Keep the vials in the outer carton in order to protect from light*.
The MAH committed to continue the ongoing stability studies throughout the proposed shelf life and to place additional commercial batches on long term stability throughout the proposed shelf life up to 36 months and on accelerated studies for 6 months.

In-use stability

Stability data has been provided demonstrating that the product remains stable for 24 hours following dilution with several commonly used solutions for infusion, when stored in glass or polyethylene containers protected from light.

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.

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

Ciprofloxacin-hameln 2 mg/ml is a parenteral formulation for use in aqueous solution and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Ciprofloxacin-hameln 2 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 MAH adopted the established Article 30 referral text (CHMP opinion in July, Commission Decision dated 7 October 2008).

Readability test
The MAH adapted the PIL to the Article 30 referral text. No user testing on content of the harmonized PIL was deemed necessary. However, the MAH was requested to align the layout of the PIL to the layout of one that has previously been tested. The MAH provided a bridging report to the user test as carried out for Alfentanil 5 mg/ml solution for injection. Layout and visual presentation are consistent and identical, and since the adopted PIL follows contents of the Article 30 referral text, bridging is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ciprofloxacin-hameln 2 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Ciproxin solution for infusion. Ciproxin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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

The SPC, package leaflet and labelling are in the agreed templates and consistent with those of the reference product.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ciprofloxacin-hameln 2 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 September 2009. Ciprofloxacin-hameln 2 mg/ml, solution for infusion was authorised in the Netherlands on 20 April 2010.

A European harmonised birth date has been allocated (31 January 1987) and subsequently the first data lock point for ciprofloxacin is January 2010. The first PSUR will cover the period from September 2009 to January 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 September 2014.

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

<u>Quality - medicinal product</u>

- The MAH committed to continue the ongoing stability studies throughout the proposed shelf life and to place additional commercial batches on long term stability throughout the proposed shelf life up to 36 months and on accelerated studies for 6 months.

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