

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Levofloxacin Fresenius Kabi 5mg/ml, solution for infusion
Fresenius Kabi Nederland B.V., Belgium**

levofloxacin (as hemihydrate)

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/1308/001/DC
Registration number in the Netherlands: RVG 102216**

25 January 2010

Pharmacotherapeutic group:	fluoroquinolones
ATC code:	J01MA12
Route of administration:	intravenous
Therapeutic indication:	infections due to levofloxacin-susceptible microorganisms, in adults
Prescription status:	prescription only
Date of authorisation in NL:	24 June 2009
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, DE, EL, ES, FI, HU, IE, IT, MT, PT, RO, SI, 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 Levofloxacin Fresenius Kabi 5mg/ml, solution for infusion, from Fresenius Kabi Nederland B.V. The date of authorisation was on 24 June 2009 in the Netherlands.

In adults for whom intravenous therapy is considered to be appropriate, the product is indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Community-acquired pneumonia.
- Complicated urinary tract infections including pyelonephritis.
- Chronic bacterial prostatitis.
- Skin and soft tissue infections.

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

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin. As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV. The degree of the bactericidal activity of levofloxacin depends on the ratio of the area under the curve (AUC) and the minimal inhibitory concentration (MIC). The main mechanism of resistance is due to a gyr-A mutation. In vitro there is a cross-resistance between levofloxacin and other fluoroquinolones. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tavanic IV, 5 mg/ml solution for infusion (NL license RVG 21810) which has been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 9 December 1997. In addition, reference is made Tavanic IV 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. As Levofloxacin Fresenius Kabi 5mg/ml is a product for aqueous parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its 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, 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 levofloxacin, an established active substance. It is not described in the European Pharmacopoeia (Ph.Eur.*). Levofloxacin is the S-enantiomer of the racemate Ofloxacin. Ofloxacin is described in the Ph.Eur.

Levofloxacin hemihydrate is an almost white to light yellow crystalline powder, soluble in methylene chloride and acetic acid and sparingly soluble in water. Levofloxacin can potentially exist in different hydrate (pseudopolymorphic) forms. Only levofloxacin hemihydrate is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture

Levofloxacin is manufactured in two production steps. A complete list of potential residual solvents is included. No class 1 solvents are used in the manufacture. The active substance has been adequately characterized and an acceptable specification has been set for the starting material and solvents.

Quality control of drug substance

The drug substance specification has been established in-house by the MAH. The specification includes test for description, identification, solubility, water content or loss on drying, specific optical rotation, sulphated ash, heavy metals, related substances, assay, XRD, chiral impurity (R(+)) and residual solvents. The specification is acceptable. The MAH committed to provide validation data of the method for the detection of N-methyl piperazine content in the drug substance. Batch analytical data demonstrating compliance with the drug substance specification have been provided for five production-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for four production-scale batches stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The batches were adequately stored. No significant changes or clear trends are seen during the stability studies. A re-test period of 2 years could be granted. No additional storage condition is necessary.

* *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

Levofloxacin Fresenius Kabi 5mg/ml contains as active substance 5 mg per ml of levofloxacin as levofloxacin hemihydrate. The product is a yellow to greenish yellow solution.

The solution for infusion is packed in a low-density polyethylene container (bottlepack) of 100 ml, closed with a cap containing a rubber disc. The 100 ml low-density polyethylene container is available in filling volumes of 50 ml or 100 ml.

The excipients are: sodium chloride, sodium hydroxide for pH adjustment, hydrochloric acid for pH adjustment, water for injection.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the formulation development was to develop an essentially similar product to the innovator product.

The pharmaceutical development of the product has been adequately performed. Neither manufacturing nor stability overages are employed during the manufacture of the drug product. The choice of sterilisation process, a non-pharmacopoeial method, is adequately justified. The pH is between 4.5 and 5.3.

Comparative studies were performed with the reference product Tavanic® in order to evaluate the comparability of Levofloxacin 5 mg/ml Solution for Infusion manufactured at Fresenius Kabi and the originator product with regard to:

- physico-chemical characteristics
- assay and most importantly
- impurity profile.

Both products are adjusted to the same isotonic osmolarity range with NaCl.

Manufacturing process

The manufacturing of the drug product levofloxacin solution for infusion consists of 7 steps, including weighing of ingredients, preparation of solution, the filling into PE containers, sterilization, inspection of sterilized containers, labeling and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four batches. Degassing of the solution with nitrogen is not considered as the product turned out to be not sensitive to oxygen. The sterilization process used is acceptable, although the product is sterilised by a non-pharmacopoeial method. The manufacturing process is, therefore, regarded as non-standard. The MAH committed to submit validation results on full-scale batches when available.

Excipients

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

Quality control of drug product

The product specification includes tests for clarity of solution, degree of coloration, extractable volume, pH value, identification and assay of levofloxacin, impurities, weight loss, subvisible and visible particles, bacterial endotoxins and sterility.

The release and shelf life criteria are similar, except for the limits for assay and one impurity. Moreover, the shelf-life specification includes an additional test for weight loss. Batch analytical data from the proposed production site have been provided on three pilot-scale batches and four full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three full-scale batches stored at 25°C/60%RH (18 months), 30°C/65%RH (12 months) and 40°C/<25%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 100 ml bottlepacks (LDPE).

The stability data for the drug product show that for all batches the results of the parameters tested meet the acceptance criteria for all parameters and are well within the specification limits. Also, no clear trends are observed, except for weight loss. However, this is not considered a significant change. The proposed shelf life of 24 months could be granted, with the storage condition '*Store in original container in order to protect from light*'.

Compatability/In-use stability

Compatibility studies have been performed with solvents included in the innovator product's SPC. The aim was to prove the compatibility with standard intravenous solutions in two different concentrations of levofloxacin in each standard solution.

For that purpose Levofloxacin Fresenius Kabi 5mg/ml was diluted to 0.5 mg/ml (100 ml diluted to 1000 ml) and 2.0 mg/ml (100 ml diluted to 250 ml) with the respective standard solutions:

- Glucose 5%
- Glucose-Ringer 2.5%
- Sodium chloride 0.9%

- Amino acid solution e.g. Aminoven 3.5GE

The diluted drug product solutions, which were stored at room temperature, were analysed after 0 and 3 hours. The product was demonstrated to be compatible and physico-chemically stable with the tested standard infusion solutions over a period of 3 hours at room temperature.

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 Tavanic IV solution for infusion, 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 levofloxacin 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

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

Levofloxacin Fresenius Kabi 5mg/ml, solution for infusion is a parenteral formulation 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 Levofloxacin Fresenius Kabi 5mg/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

Levofloxacin was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of levofloxacin 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

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. Male and female representative subjects over the age of 22-77 years were chosen as target population. The inclusion/exclusion criteria were acceptable.

The leaflet was tested by interviewing each subject, noting the time required to find the information and also giving the correct answer in their own words. A questionnaire with 15 questions was used. Fourteen questions addressed the content of the package leaflet (what the product is used for, how the product is

used, important questions concerning product's safety i.e. recognition of adverse events, the use with other medicines, contra indication and pregnancy). The last question was an open question to investigate the subjects' opinion about the lay-out of the PIL.

Based on the pilot test results, a modification with regard to question 9 was made, for the interviewed subjects had some difficulties understanding the question.

In the first test round, 90% of the participants were able to find the information requested and gave a correct answer. Three questions were not found by a few subjects. No major changes were made. For one question the order of the sentence was modified. Although satisfactory results were obtained for 2 other questions, slight modifications were introduced.

In the second round of testing, again the 90% criterium was met. The three answers not found came from one individual. The MAH considered this result as not representative for the test, since the other nine people did not experience any problems with these questions.

Regarding the content of the package leaflet, 95% said that their understanding of the package leaflet was good, although 80 % said that it contained too much technical language which makes it difficult to understand. The clarifications in brackets after the technical terms helped them understand the terms.

The lay-out, structure, table of content and bold titles were positively commented on by the participants. It helped them find the information much faster.

In conclusion, the proposed package leaflet can be considered to meet the required readability standards. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levofloxacin Fresenius Kabi 5mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Tavanic IV, 5 mg/ml solution for infusion. Tavanic IV 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. One commitment has been made, which can be found below.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other levofloxacin containing products.

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 Levofloxacin Fresenius Kabi 5mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 30 January 2009. Levofloxacin Fresenius Kabi 5mg/ml, solution for infusion was authorised in the Netherlands on 24 June 2009.

A European harmonised birth date has been allocated (1 October 1993) and subsequently the first data lock point for levofloxacin is October 2009. The first PSUR will cover the period from January 2009 to October 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 January 2014.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH committed to provide validation data of the method for the detection of N-methyl piperazine content in the drug substance. This commitment has been fulfilled.

Quality - medicinal product

- The MAH committed to perform validation studies on the first three commercial batches with the maximum batch size, and to present the results to the competent authorities. Until this has been fulfilled, a smaller maximum will apply.

Pharmacovigilance system

- The MAH committed to have the SOP with regard to 'Meeting commitments to Competent Authorities in relation to a marketing authorisation' in place before the product is marketed.

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
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
t _{1/2}	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