CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levofloxacine Mylan 250 mg, film-coated tablets
Levofloxacine Mylan 500 mg, film-coated tablets
Mylan B.V., the Netherlands

levofloxacin 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/1129/001-002/DC
Registration number in the Netherlands: RVG 100261, 100262

26 October 2009

Pharmacotherapeutic group:	fluoroquinolones
ATC code:	J01MA12
Route of administration:	oral
Therapeutic indication:	infections of mild or moderate severity due to levofloxacin-susceptible microorganisms, in adults
Prescription status:	prescription only
Date of authorisation in NL:	3 July 2009
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, EL, ES, FI, HU, IE, IT, PT, SE, SK, 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 Levofloxacine Mylan 250 mg and Levofloxacine Mylan 500 mg, film-coated tablets, from Mylan B.V.. The date of authorisation was on 3 July 2009 in the Netherlands.

The product is indicated in adults with infections of mild or moderate severity, for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute bacterial sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections)
- Acute bacterial exacerbations of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections)
- 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 250 and 500 mg tablets (NL License RVG 21811 and 21812 respectively), which have been registered in the United Kingdom by Hoechst Marion Roussel Ltd. since 1997. In addition, reference is made to Tavanic 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Tavanic® 500 mg film-coated 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. This generic 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.

No paediatric development programme has been submitted because this is not required for a generic product.

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 these product types 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.
For manufacturing sites within the Community, the MEB has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the MEB has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Active substance

General information
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 and this is controlled in the drug substance specification with a test for water content.

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/EMEA 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.

** 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.*

Manufacture
Levofloxacin hemihydrate is prepared via a two-step synthesis. Information on the supplier and synthesis of the starting material have been provided. In general acceptable specifications for the raw materials have been adopted.

Specification
The drug substance specification includes tests for appearance, solubility, identification (IR, HPLC), water, heavy metals, residue on ignition, clarity of solution, specific optical rotation, related substances, assay, residual solvents, chiral purity and particle size. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. The limit for 'particle size' is acceptable in view of the particle size of the biobatch used in the bioequivalence studies. The requirements for residual solvents are acceptable in view of ICH Q3C. All analytical methods have been sufficiently described. Batch analytical data have been provided for 3 batches. All of these showed compliance with the specifications.

Stability of drug substance
Stability data have been obtained during storage at 25°C/60% RH and 40°C/75% RH. The drug substance was packaged in the commercial packaging, i.e. double PE bag in a blue HDPE container. The solid drug

substance seems to be stable. However, a chiral purity parameter was not included. The MAH committed to include a test for chiral purity in the stability program for all future batches placed on stability. A retest period of 2 years could be granted if stored in light-resistant containers. The MAH commited to provide additional stability results, at least covering the granted retest period for in total three production batches.

Medicinal Product

Composition
Levofloxacine Mylan 250 mg film-coated tablets contain as active substance 250 mg of levofloxacin as levofloxacin hemihydrate, and are white to off-white, capsule shaped, biconvex, film-coated tablet, debossed with “LVO” scoreline “250” on one side and “G” scoreline “G” on the other side. The tablet can be divided into equal halves.

Levofloxacine Mylan 500 mg film-coated tablets contain as active substance 500 mg of levofloxacin as levofloxacin hemihydrate, and are white to off-white, capsule shaped, biconvex, film-coated tablets, debossed with “LVO” scoreline “500” on one side and “G” scoreline “G” on the other side. The tablet can be divided into equal halves.

The excipients are, for both the 250 mg and 500 mg strengths:

Tablet core:
Microcrystalline cellulose (Avicel pH 101 and pH 112) (E460)
Crospovidone (E1202)
Hydroxypropyl cellulose (E463)
Magnesium stearate (E470b)

Tablet coating:
Hydroxypropyl cellulose (E463)
Macrogol 400
Macrogol 3350
Titanium dioxide (E171)

Both tablets are completely dose proportional.

Pharmaceutical development
The product is an established pharmaceutical form and the development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of film-coated tablets. The used excipients are safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs. The drug product is packed in PVC/aluminium foil blisters or HDPE containers with polypropylene closures. Specifications and test methods are described for all parts of the packaging. The packagings are usual and suitable for the product at issue.

Manufacturing process
The manufacturing process comprises the formation of Levofloxacin granules through a conventional blending and roller compaction process and production of a final blend, followed by tablet compression and film-coating. Process validation studies have been performed on two pilot batches of each strength of the proposed product. The process has been sufficiently validated on pilot scale. The MAH committed to perform formal process validation studies on the first 3 production-scale batches of each strength of the proposed products. This process validation will be performed on the maximum batch scale.

Quality control of the medicinal product
The drug product specification includes tests for appearance, identity (ID drug substance and ID titanium dioxide), uniformity of dosage units, assay, dissolution, water content, related substances, residual solvents, breakability and microbiology. The specification at release and at the end of shelf-life is the same.
All in-house analytical procedures have been adequately described.

Validation reports have been included for the HPLC tests on assay/identification and related substances, the dissolution method and the GC test on ethanol. For all other analytical procedures the MAH states compliance with the Ph.Eur., except for the identification test for titanium dioxide as this test is a colour change test for which validation data are not considered necessary. This was found acceptable. Studies have been performed and indicate that the polymorphic form of the drug substance remains unchanged during manufacture of the finished product and that the active substance is consistent with XRPD spectra of the relevant levofloxacin hemihydrates form.
Batch analysis data have been provided on two pilot batches of each strength. Compliance with the release requirements is demonstrated. The MAH committed to provide batch analysis results of the first three production-scale batches.

Stability tests on the finished product
Stability data on the product have been provided for two pilot scale batches of each strength stored at 25ºC/60%RH, 30ºC/65%RH and 40ºC/75%RH. The results were all within specification. No distinct trends have been observed for the parameters tested. Photostability has been demonstrated; no differences have been observed between the drug product exposed to light and stored in dark. A shelf-life of two years without special storage conditions has been granted. The MAH committed to place the first three production scale batches of both strengths on stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is derived from material of vegetable origin. There are no other 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

These products are generic formulations of Tavanic 250 and 500 mg tablets, which are 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.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Levofloxacine Mylan 500 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Tavanic® 500 mg film-coated tablets from the German market.

Test and reference products
The reference product is considered acceptable. The difference in content of active substance for Reference and Test is less than 5%. This difference was not taken into account in the pharmacokinetic or statistical analysis. The batch size of the test tablets is in line with the guidelines, in which a batch size is requested of at least 100.000 tablets and over 1/10th of the commercial batch size.

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 analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Design
A single-dose, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (11 males and 13 females), aged 22-54 years. All subjects were non smokers. Each subject received a single dose (500 mg) of one of the 2 levofloxacin formulations. The tablet was orally administered in solid form with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 14 days. Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 6, 8, 12, 16, 24, and 36 hours after administration of the products. One subjects withdrew for personal reasons. The remaining 23 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=23	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	57.6 ± 16.1	59.2 ± 16.7	6.11 ± 1.67	1.25 (0.75 - 4.0)	6.6 ± 0.8
Reference	56.4 ± 16.8	57.9 ± 17.4	6.14 ± 1.57	1.25 (0.5 - 4.0)	6.6 ± 0.8
***Ratio (90% CI)**	1.02 (0.99 - 1.06)	1.02 (0.99 - 1.06)	0.99 (0.93 - 0.95)	-	-
CV (%)	5.5	6.3	10.9	-	-

$AUC_{0-\infty}$ 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*

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

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 levofloxacin under fasted conditions, it can be concluded that Levofloxacine Mylan 500 mg film-coated tablets and reference Tavanic® 500 mg film-coated 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 Levofloxacine Mylan 500 mg film-coated tablets are dose proportional with the 250 mg film-coated tablets. The tablets have been manufactured by the same manufacturing process. In addition, levofloxacin shows linear pharmacokinetics over the 50-600 mg dose range. Taking into account the comparable dissolution profiles, the results of the bioequivalence study performed with the 500 mg film-coated tablets therefore apply to the other strength.

GCP and GLP
The MEB has been assured that the bioequivalence study has 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).

CMD(h)
At day 145 one of the concerned member states raised major health concerns and proposed to further restict the indications acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP). There was also a concern with regard to the use of levofloxacin in the treatment of MRSA. The rationale for these concerns is a CHMP referral (Article 107) procedure regarding the use of oral formulation of moxifloxacin containing medicines. A CHMP opinion was reached in July 2008, resulting in a restricted use of oral moxifloxacin in the questioned indications. One of the concerned member states argued that the situation for moxifloxacin is similar for levofloxacin and therefore the same restrictions on the sought indications should be implemented for levofloxacin oral formulations.
By day 210, there was no agreement between the member states. A CMD referral procedure was started. The referral was discussed in the CMD(h) of January 2009. The RMS presented its view and the MAH's written response was discussed. The outcome resulted in further restriction of these indications in the SPC. It was agreed to harmonise this SPC and PIL with regard to the indications to the SPC and PIL for levofloxacin agreed in FI/H/0697/001-002/MR and FI/H/0698/001-002/MR. A warning is added to section 4.4 to mention that levofloxacin is not effective in the treatment of infections caused by MRSA.
After consultation with the EMEA, it was agreed to refer the originator according to Article 36 for a benefit/risk assessment of the indications. Member states where the product is authorised via national procedure should follow the outcome of the referral to keep the SPC harmonised.

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 post authorisation 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 decentralised procedure is in accordance with that accepted for the reference product Tavanic marketed by Sanofi Aventis. However, following the CMD referral procedure, the indications in section 4.1 have been restricted and a warning has been added to section 4.4.

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, followed by two rounds with 10 participants each. Twelve questions were asked, covering the following areas sufficiently: traceability, comprehensibility and applicability. Also, the participants were asked for comments about the leaflet (content and laly-out). The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levofloxacine Mylan 250 mg film-coated tablets and Levofloxacine Mylan 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Tavanic 250 and 500 mg tablets. Tavanic 250 and 500 mg tablets are well-known medicinal products 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 Board followed the advice of the assessors.

During the decentralised procedure no consensus was reached at day 210, 26 October 2008, regarding the benefit/risk profile of the indications acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (AECB), and community-acquired pneumonia (CAP). There was also a concern with regard to the use of levofloxacin in the treatment of MRSA. Therefore, the procedure was referred to the CMD(h).

In the CMD(h) meeting of 19 January 2009, the following was discussed:
The RMS presented its view and the MAH's written response was discussed. The CMD(h) decided to harmonise the SPC and PIL with regard to the indications to the SPC and PIL agreed in FI/H/0697/001-002/MR and FI/H/0698/001-002/MR. A warning was added to section 4.4 to mention that levofloxacin is not effective in the treatment of infections caused by MRSA. The CMD(h) referral ended positively on 26 January 2009. Levofloxacine Mylan 250 mg film-coated tablets and Levofloxacine Mylan 500 mg film-coated tablets were authorised in the Netherlands on 3 July 2009.

The SPC is consistent with that of the reference product, except for the indications (ABS, AECB and CAP) mentioned above. These were restricted in line with the SPC for FI/H/0697/001-002/MR and FI/H/0698/001-002/MR. Also, a warning on the ineffectiveness of the product in the treatment of infections caused by MRSA was added. The SPC, package leaflet and labelling are in the agreed templates.

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 registration to October 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 26 January 2014.

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

Quality - active substance
- The MAH committed to include a test for chiral purity in the stability program for all future batches placed on stability.
- The MAH committed to provide additional stability results, at least covering the granted retest period for in total three production batches.

Quality - medicinal product
- The MAH committed to perform formal process validation studies on the first 3 production-scale batches of each strength of the maximum batch scale.
- The MAH committed to provide batch analysis results of the first three production-scale batches.
- The MAH committed to place the first three production scale batches of both strengths on stability.

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
HPLC	High Performance, Liquid Chromatography
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