

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

**Levofloxacin Aurobindo 250 mg and 500 mg, film-coated tablets
Aurobindo Pharma B.V., the Netherlands**

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.

It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 107787, 107790

21 January 2013

Pharmacotherapeutic group:	quinolone antibacterials, fluoroquinolones
ATC code:	J01MA12
Route of administration:	oral
Therapeutic indication:	infections of mild or moderate severity due to levofloxacin-susceptible microorganisms, in adults (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	17 June 2011
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Levofloxacin Aurobindo 250 mg and 500 mg, film-coated tablets from Aurobindo Pharma B.V. The date of authorisation was on 17 June 2011 in the Netherlands.

The product is indicated for:

- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections.

For the above-mentioned infections Levofloxacin Aurobindo should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

- Pyelonephritis and complicated urinary tract infections including
- Chronic bacterial prostatitis
- Uncomplicated cystitis
- Inhalation Anthrax: postexposure prophylaxis and curative treatment

Levofloxacin Aurobindo may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.

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.

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 national procedure concerns a generic application claiming essential similarity with the innovator products Tavanic 250 and 500 mg tablets (NL License RVG 21811-21812), which have been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 9 December 1997.

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 tablet, registered in the UK. 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 and no paediatric development programme has been submitted, as 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 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 hemihydrate, an established active substance. It is not described in the European Pharmacopoeia (Ph.Eur.*). It is a pale or bright yellow crystalline powder that is freely soluble in glacial acetic acid and chloroform, sparingly soluble in methanol, slightly soluble in ethanol and practically insoluble in ether. Levofloxacin hemihydrate is the (-)-S-isomer of ofloxacin. Levofloxacin can potentially exist in different hydrate (polymorphic) forms; the hemihydrate form is used.

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.

Manufacturing process

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

Quality control of drug substance

The drug substance specification includes appropriate tests. The specification is acceptable in view of the route of synthesis and the various ICH guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

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. Based on the data obtained, the proposed retest period of 36 months without special storage conditions can be granted.

* *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

The 250 mg tablets are pink coloured, capsule shaped, biconvex film-coated tablets debossed with '1' and '5' on either side of score line on one side and 'T' on the other side. The 500 mg tablets are pink coloured,

capsule shaped, biconvex film-coated tablets debossed with '1' and '4' on either side of score line on one side and 'T' on the other side. The tablets can be divided into equal halves.

The film-coated tablets are packed in PVC/Aclar-Alu blister and an opaque HDPE bottle with PP closure.

The excipients are: microcrystalline cellulose, croscarmellose sodium, hypromellose, magnesium stearate, and the Ready to use coating agent (hypromellose, titanium dioxide, macrogol, talc, iron oxide yellow, iron oxide red).

Both strengths are fully dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The solvent in the wet-granulation process is purified water. The subdivision of both tablets (250 mg and 500 mg) was tested on 3 batches of each strength and complies with the relevant Ph.Eur. monograph.

The dissolution method has been adequately developed in order to show similarity of dissolution profiles between the reference and test products. The composition of the biobatch was identical to the proposed commercial composition. The NL originator product has been registered through Mutual Recognition Procedure UK/H/0203/01-02. Herewith the UK 500 mg reference product used in the bio-equivalence study is representative of the innovator product on the market in the Netherlands. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is divided into the following steps: sifting, dry mixing, wet granulation, drying, dry milling, sifting, mixing, lubrication, compression, coating and drying, packaging.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial-scale batches of granules. These batches were each divided into two batches of each strength tablets. The product is manufactured using conventional manufacturing techniques. Process validation for larger batches sizes will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. or NF requirements. The ready to use coating material complies with in-house specification. Two grades of microcrystalline cellulose are used (different particle sizes) and they are tested for bulk density and starch. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification of levofloxacin, identification of colourants, average mass, subdivision of tables, water content, dissolution, uniformity of dosage units (mass variation), related substances, assay, thickness and microbial limits. Hardness and friability are tested as in-process controls and not part of the release specification. The release and shelf-life limits are identical except for water content, related substances and assay. The limits are acceptable. The analytical methods have been adequately described and validated, and are stability indicating.

Batch analytical data have been provided on three commercial-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three commercial-scale batches stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging (blister and both bottle sizes) and simulated bulk packaging (LDPE bag). An increase impurities was observed, but all test results remained within specification. The product is not sensitive to light. The proposed shelf-life of 24 months without special storage conditions is acceptable.

Stability data has been provided demonstrating that the product remains stable for 3 months following first opening of the HPDE container, when stored at 25°C/60% RH.

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. Magnesium stearate used is of vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Tavanic, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

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.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Levofloxacin Aurobindo 500 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Tavanic 500 mg film-coated tablets (Sanofi-Aventis, UK).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-42 years. Each subject received a single dose (500 mg) of one of the 2 levofloxacin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30 and 36 hours after administration of the products.

Analytical/statistical methods

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

Results

One subject did not show up for Period II. Twenty-seven subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=27	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	45.8 \pm 7.7	48.7 \pm 7.8	5.60 \pm 1.33	1.0 (0.5 – 2.5)	7.7 \pm 1.0
Reference	45.3 \pm 7.2	48.2 \pm 7.5	5.32 \pm 0.98	1.0 (0.5 – 3.0)	7.7 \pm 0.9
*Ratio (90% CI)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.04 (0.97-1.10)	--	--
CV (%)	4.0	4.0	13.7	--	--
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Levofloxacin Aurobindo 500 mg and 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.

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.

Extrapolation to 250 mg

The Levofloxacin Aurobindo 500 mg film-coated tablets are dose proportional with the 250 mg film-coated tablets. The tablets are manufactured by the same manufacturing process. In addition, levofloxacin shows linear pharmacokinetics over the 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.

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).

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 national procedure is in accordance with that accepted for the reference product Tavanic.

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 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both test rounds, for each question 90% of all participants were able to find the information requested within the PIL, and 90% of all participants showed that they understand and would be able to act upon it. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levofloxacin Aurobindo 250 mg and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Tavanic 250 and 500 mg tablets. Tavanic 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 SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Levofloxacin Aurobindo 250 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 17 June 2011.

There were no post-approval commitments made during the procedure.

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 _{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
Transfer of the marketing authorisation.	--	MA transfer	2-8-2011	22-8-2011	Approval	N
Change in batch size of active substance (up to 10-fold increase compared to the currently approved batch size).	--	IA	28-12-2011	27-2-2012	Approval	N
Update of the SPC and PL of Levofloxacin Aurobindo 250 mg/500 mg film-coated tablets in line with referral procedure following a safety variation to the Marketing Authorisation of Tavanic as accepted by CHMP and also in line with version 8 of the QRD template.	--	IB	8-10-2012	16-11-2012	Approval	N