**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Levofloxacin 5mg/ml Solution for infusion, Non PVC bag
Levofloxacin hemihydrate
PA2299/040/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

**CONTENTS**

## I. INTRODUCTION

This product was initially authorised under procedure number UK/H/1976/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 05/12/2018 under procedure number IE/H/0868/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2299/040/001-002
Marketing Authorisation Holder: Baxter Holding BV

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Levofloxacin 5 mg/ml Solution for Infusion in the treatment of bacterial infections could be approved.

This application was submitted under Article 10.1, claiming to be generic medicinal product of Tavanic 5 mg/ml solution for infusion (PL 13402/0013), which was first licensed in the UK to Hoechst Marion Roussel Ltd, on 6th June 1997.

With UK as the RMS in this Decentralised Procedure (UK/H/1976/001/DC), Claris Lifesciences UK Limited applied for the Marketing Authorisation for Levofloxacin 5 mg/ml Solution for Infusion in the following CMSs:

Belgium, Germany, France, Italy, Latvia, Luxemburg, Portugal, Republic of Ireland and The Netherlands.

The fluoroquinolones are a group of synthetic, broad-spectrum antibiotics with bactericidal activity. Levofloxacin is a third generation fluoroquinolone, with enhanced activity against Gram-positive organisms, and is the active S-enantiomer of D-ofloxacin. Levofloxacin binds to the A subunit of deoxyribonucleic acid (DNA) gyrase and DNA topoisomerase IV in bacteria, and causes defective supercoiling of DNA and also impairment of relaxation of supercoiling in chromosomes and plasmids. It exhibits high potency *in vitro* and a long elimination half-life, thus permitting once-daily dosing. Although the rate of resistance to other antibiotic classes has grown, levofloxacin has maintained efficacy with generally very low rates of resistance world-wide.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of the originator product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within and outside the Community, the RMS 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.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for the non-submission of a Risk Management Plan.

All member states agreed to grant a licence for the above product at the end of the procedure (Day 210 – 7th June 2012). After a subsequent national phase, the UK granted a licence for this product on 18th July 2012 (PL 20568/0027).

## II. QUALITY ASPECTS

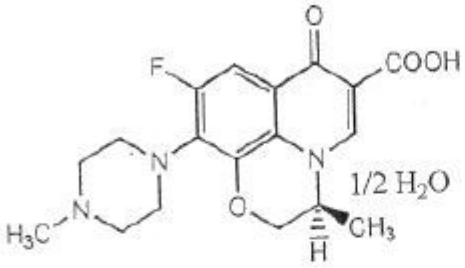
# III SCIENTIFIC OVERVIEW AND DISCUSSION

## III.1 QUALITY ASPECTS

### DRUG SUBSTANCE

INN: Levofloxacin hemihydrate
Chemical Names: (-)-(s)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3, -de]-1,4 benzoxazine-6-carboxylic acid hemihydrate.

Structure:




Molecular formula: $C_{18}H_{20}FN_3O_4.½H_2O$

Molecular weight: 370.38

Physical form: Light yellowish-white odourless powder.
Solubility: Sparingly soluble in methanol, aqueous solubility decreases with increase in pH

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

### DRUG PRODUCT

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients sodium chloride, hydrochloric acid, sodium hydroxide and water for injection.

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the pharmaceutical development programme was to obtain a stable product containing levofloxacin hemihydrate that could be considered a generic medicinal product of Tavanic 5 mg/ml Solution for Infusion (Hoechst Marion Roussel Limited).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.

**Manufacture**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

**Finished Product Specifications**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The finished product is supplied in:

Bottle
Type I glass bottle with aluminium cap, bromobutyl rubber stopper and flip off seal. Packs of 1, 5, and 10 x 100 ml bottles are available.

Bag
100 ml Non polyvinylchloride(PVC) bag consists of Non PVC Film, Non PVC Tube, Spike Port and EMP White Elastomer closure. Each bag contains 100 ml of solution for infusion. Packs of 1, 5, and 10 x 100 ml bags are available.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf life of 2 years for packaged for sale and after removal of the outer carton/overwrap pouch – to be used immediately are set.

Shelf life after perforation of the rubber stopper: (see section 6.6 of the SPC).

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

The storage conditions are "Do not freeze" and "Keep bottle/bag in the outer carton/over wrap pouch in order to protect from light". These are satisfactory.

**Bioequivalence/bioavailability**
No bioequivalence studies have been submitted and none are required to support an application of this type.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended, and is well structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The marketing authorisation holder has stated that not all packs are intended to be marketed. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

**Marketing Authorisation Application (MAA) Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of this product from a pharmaceutical point of view.

## III. NON-CLINICAL ASPECTS

### III.2 NON-CLINICAL ASPECTS
### PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties levofloxacin hemihydrate are well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for the non-submission of the environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

## IV. CLINICAL ASPECTS

### III.3 CLINICAL ASPECTS

*Pharmacokinetics*

In accordance with Note for Guidance on the investigation of bioavailability and

bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with this application and none is required.

No new data have been submitted and none are required for applications of this type.

*Pharmacodynamics*
No new data have been submitted and none are required for applications of this type.

*Clinical efficacy*
No new data have been submitted and none are required for applications of this type.

*Clinical safety*
Levofloxacin hemihydrate has an acceptable adverse event profile. No new safety data were supplied or required for this generic application. Levofloxacin hemihydrate has a well-established side-effect profile and is generally well-tolerated.

*Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling*
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

*Clinical Expert Report*
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

*Marketing Authorisation Application (MAA) Form*
The MAA form is medically satisfactory.

*Clinical Conclusion*
There are no objections to the approval of this product from a clinical point of view.

## V. OVERALL CONCLUSIONS

### IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

**QUALITY**
The important quality characteristics of Levofloxacin 5 mg/ml solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**
No non-clinical data were submitted and none are required for applications of this type.

**EFFICACY**
No new efficacy data were submitted and none are required for applications of this type. As the safety profile of levofloxacin hemihydrate is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory.

**BENEFIT-RISK ASSESSMENT**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levofloxacin hemihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is, therefore, considered to be positive.

## VI. REVISION DATE

28/02/2022

**VII. UPDATES**

This section reflects the significant changes following finalisation of the initial procedure.

| SCOPE | PROCEDURE NUMBER | PRODUCT INFORMATION AFFECTED | DATE OF START OF PROCEDURE | DATE OF END OF PROCEDURE |
|---|---|---|---|---|
| RMS transfer | From UK/H/1976/1/DC to IE/H/0868/1/DC | | | |