COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levonic 5 mg/ml solution for infusion (levofloxacin hemihydrate)

NL/H/5661/001/DC

Date: 16 February 2026

This module reflects the scientific discussion for the approval of Levonic 5 mg/ml solution for infusion. The procedure was finalised on 21 August 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Levonic 5 mg/ml solution for infusion, from Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.

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

- Community-acquired pneumonia
- Complicated skin and soft tissue infections

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

- Acute pyelonephritis and complicated urinary tract infections
- Chronic bacterial prostatitis
- Inhalation Anthrax: postexposure prophylaxis and curative treatment

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Tavanic 5 mg/ml solution for infusion (DE/H/5119/003/MR) which has been registered in Germany by Sanofi-Aventis AEBE since 17 February 1999.

The concerned member states (CMS) involved in this procedure were Cyprus, Greece, Finland and Norway.

II. QUALITY ASPECTS

II.1 Introduction

Levonic is a solution for infusion. The solution is clear, colourless to greenish-yellow and free of particles with pH: 4.5-5.5 and osmolality: 260-320 mOsm/kg H2O.

Each 100 ml of solution for infusion contains as active substance 500 mg of levofloxacin as levofloxacin hemihydrate.

The excipients are: sodium chloride, sodium hydroxide (E524; for pH-adjustment), hydrochloric acid (E507; for pH-adjustment) and water for injections.

The solution for infusion is packed in a 100 ml polyolefin/styrene bag with a polypropylene port and cap and polyisoprene rubber disk. The bags are presented in aluminium sachets. Each bag contains 100 ml solution for infusion.

II.2 Drug Substance

The active substance is levofloxacin hemihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a light yellowish-white or light yellow, crystalline powder and is sparingly soluble in water. The active substance is the S-enantiomer of the racemate Ofloxacin. The polymorphic form of the drug substance is not relevant as the drug substance is dissolved in the drug product.

The CEP procedure is used for 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 suitability 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and is in line with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The choice of excipients is justified and their functions explained. The aim of the formulation development was to develop generally safe, efficacious, and well tolerated product, and being a generic medicinal product of the reference product Tavanic.

Manufacturing process
The manufacturing process represents a standard process combining dissolution steps and packaging. The manufacturing process has been validated according to relevant European/ICH

guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable. The quality of water used for the preparation of the drug product for parenteral use is in accordance with the EMA Guideline on the quality of water for pharmaceutical use. These specifications are acceptable.

Microbiological attributes

The product is a sterile product. Sterility and bacterial endotoxins are controlled according to the requirements of the Ph. Eur. 2.6.1 and 2.6.14 as part of the finished product specification which is acceptable as per Ph.Eur. monograph on Parenteral Preparations 0520.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of levofloxacin hemihydrate, pH, relative density, osmolality, dissolved oxygen, extractable volume, uniformity of dosage units, particulate contamination (visible, subvisible particles), quantitative determination of levofloxacin hemihydrate, quantitative determination of related substances of levofloxacin, sterility, and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scale batches stored at 25°C/60% RH (one batch 36 months and two batches 18 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. The MAH provided sufficient details on the photostability study, which is performed as per requirements of ICH Q1B. On basis of the data submitted, a shelf life was granted of 30 months. The labelled storage conditions are “This medicinal product does not require any special temperature storage conditions. After first opening of the sachet: The bags should be stored in the sachet to protect from light”.
After finalisation of the DCP, additional data were provided and the shelf life was extended from 30 to 36 months (variation NL/H/5661/001/IB/001, see table at the end of this PAR).

No in-use stability studies are required since the drug product is packaged in a single-dose container in line with the EMA NfG on in-use stability testing of human medicinal products.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Levonic has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Levonic is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Tavanic which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Levofloxacin hemihydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the biowaiver, which is discussed below.

IV.2 Pharmacokinetics

Levonic 5 mg/ml solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Guideline on the investigation of bioequivalence "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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98 Rev.1, Corr). The quantitative composition of Levonic 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.

Biowaiver

A biowaiver is requested instead with reference to the Guideline "Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev. 1, Corr). Bioequivalence testing can be waived under the provisions of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, Appendix II, especially in the case of parenteral solutions.

The respective values for both products are in close agreement and meet the specifications, including impurity profile, relative density, surface tension, pH and osmolality. Taking into consideration all the above discussion, it can be safely supported that all the biowaiver criteria mentioned in the Guideline on the Investigation of Bioequivalence are fulfilled.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Levonic. At the time of approval, the most recent version of the RMP was version 0.2 dated 21 February 2024.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Prolonged, potentially irreversible, serious suspected adverse drug reaction that lasts 30 days or more • Aortic aneurysm and dissection and heart valve regurgitation/incompetence.
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product. No new clinical studies were conducted. Essential similarity with the reference product is based on the comparative quality attributes of the product. The product has the same qualitative and quantitative composition and the same type of solution as that of the reference product. Hence, the absence of a bioequivalence study is agreed in line with the BE guideline and the provided data is regarded sufficient to support the application. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Levonic 5 mg/ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Tavanic 5 mg/ml solution for infusion. Tavanic 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. A biowaiver has been granted.

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 Levonic with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 August 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5661/001 /IB/001	Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data).	Yes	13-10-2025	Approved	N.A.
NL/H/5661/IA/ 002/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent /intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer.	No	26-01-2026	Approved	N.A.