Public Assessment Report

Scientific discussion

Leucovorine Sandoz 10 mg/ml, solution for injection/infusion

(calcium folinate)

NL/H/3594/001/DC

Date: 24 August 2017

This module reflects the scientific discussion for the approval of Leucovorine Sandoz 10 mg/ml, solution for injection/infusion. The procedure was finalised on 2 November 2016. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
### List of abbreviations

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

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Leucovorine Sandoz 10 mg/ml, solution for injection/infusion from Sandoz B.V. Netherlands.

The product is indicated:
- to diminish the toxicity and counteract the action of folic antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, this procedure is commonly known as “Calcium Folate Rescue”;
- in combination with 5-fluorouracil in cytotoxic therapy.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ledervorin calcium 50 mg/5ml concentrate for injection/infusion which has been registered Wyeth Pharmaceuticals B.V., which was registered 4 April 1990 in the Netherlands, but withdrawn in December 2001.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Czech Republic, Germany, Denmark, Finland, France, Croatia, Hungary, Lithuania, Poland, Sweden, Slovenia, Slovak Republic and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Leucovorine Sandoz is a clear, yellowish solution for injection/infusion, practically free from turbidity and foreign matter with pH of 7.0-8.6 and osmolarity of 275 mOsm. One ml of solution for injection/infusion contains 10 mg of folinic acid provided as calcium folinate hydrate.

The solution for injection/infusion is packed in glass type I vials with a bromobutyl rubber stopper and sealed with aluminum flip-off seals.

The excipients are: sodium chloride, sodium hydroxide (for pH adjustment), dilute hydrochloric acid (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is calcium folinate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Calcium folinate is sparingly soluble in water, practically insoluble in acetone and ethanol (96%). Particle size and polymorphic form of the active substance are not deemed critical since it will be used for a solution for injection/infusion.

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 European Pharmacopoeia.

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 is fully in line with the CEP. Batch analytical data demonstrating compliance with this specification have been provided for 1 full scale batch.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scale batches stored at 25°C/60% RH (up to 60 months), 40°C/75% (6 months), 2 – 8°C (up to 60 months) and -20°C (up to 60 months). On basis of the data submitted, a re-test period has been granted of 24 months if stored at 2-8°C.

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 compatibility with different infusion solutions has been investigated. A bioequivalence study has not been performed since it concerns an aqueous solution for injection and infusion containing the same (quantitatively and qualitatively) active substance as the originator product Ledervorin calcium. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. It is a straight-forward process, consisting of preparation of the bulk solution, two sterile filtrations, filling and packaging. Process validation data on the product have been presented for 3 full scaled batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph. Eur. These specifications are acceptable.

Microbiological attributes
Calcium folinate 10 mg/ml, solution for injection/infusion is a sterile dosage form without preservatives. The medicinal product is tested according to the requirements of the Ph. Eur. for such parenteral dosage forms.

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 description, extractable volume, appearance of solution (clarity and coloration), identity (calcium folinic acid), pH, particulate contamination, assay, related substances, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data 14 full scaled 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 12 full scaled batches stored at 2–8°C (12-30 months) and stored at 25°C/60% RH (6 months). The conditions used in the stability studies are accordance with the ICH stability guideline. The batches were stored in the proposed packaging. The results of the photostability study show no sensitivity to light. On basis of the data submitted, a shelf life was granted of 24 months when stored in a refrigerator (2-8°C).

Chemical and physical in-use stability has been demonstrated for 28 days at 2°C to 8°C after dilution with sodium chloride 0.9% to concentrations of 0.2 mg/ml and 4.0 mg/ml. Chemical and physical in-use stability has been demonstrated for 4 days at 2°C to 8°C after dilution with glucose 5% to a concentration of 0.2 mg/ml and for 28 days at 2°C to 8°C after dilution to a concentration of 4.0 mg/ml. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
Specific measures for 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 Leucovorine Sandoz 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 Leucovorine Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ledervorin calcium. Reference is made to the preclinical data obtained with the innovator product. 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Calcium folinate 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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Leucovorine Sandoz 10 mg/ml, solution for injection/infusion is a parenteral formulation 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Leucovorine Sandoz 10 mg/ml, solution for injection/infusion 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.

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 Leucovorine Sandoz.

- Summary table of safety concerns as approved in RMP
Important identified risks
- Hypersensitivity
- Interaction with folic acid antagonists
- Enhanced risk of toxicity of 5-fluorouracil, particularly in elderly or debilitated patients
- Impairment of antitumor activity of MTX with high dose of Calcium Folate
- Drug interaction with phenobarbital, phenytoin, primidone, and succinimides resulting in increased frequency of seizures in epileptic patients
- Masking of Pernicious anemia or other anemias due to vitamin B12 deficiency

Important potential risks
- Risk of death from intrathecal route of administration

Missing information
- Use in pregnant or breast-feeding women

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 Ledervorin calcium. No new clinical studies were conducted. The MAH demonstrated that the quantitative composition of the product is similar to the quantitative composition of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to a test on same class of medicinal product. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Leucovorine Sandoz 10 mg/ml, solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Ledervorin calcium 50 mg/5ml concentrate for injection/infusion. Ledervorin calcium 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 and contain the same active substance in the same concentration, no bioequivalence study is deemed necessary.

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 Leucovorine Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 November 2016.
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