COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ciprofloxacine Altan 2 mg/ml, solution for infusion

(ciprofloxacin)

NL/H/4292/001/DC

Date: 25 July 2019

This module reflects the scientific discussion for the approval of Ciprofloxacine Altan 2 mg/ml, solution for infusion. The procedure was finalised at 27 February 2019. 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
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
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 Ciprofloxacine Altan 2 mg/ml, solution for infusion, from Altan Pharma Ltd.

The product is indicated for the treatment of the following infections. Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Adults

- Lower respiratory tract infections due to Gram-negative bacteria:
  - exacerbations of chronic obstructive pulmonary disease
  - broncho-puimonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to susceptible *Neisseria gonorrhoeae*. In infections of the genital organs that are thought or known to be caused by *Neisseria gonorrhoeae*, it is very important to obtain local information regarding the prevalence of resistance to ciprofloxacin and to confirm susceptibility with appropriate microbiological tests.
- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in patients with neutropenia
- Prophylaxis of infections in patients with neutropenia
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*.
- Complicated urinary tract infections and pyelonephritis.
- Inhalation anthrax (post-exposure prophylaxis and curative treatment).

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

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 Ciprofloxacino Anages 2 mg/ml solution for infusion which has been registered in Spain by G.E.S. Genéricos Españoles Laboratorio S.A. since 1 February 1989. As no registration of solution for infusion containing ciprofloxacin has been granted in the Netherlands, the Spanish product is used as European Reference Product.

The concerned member states (CMS) involved in this procedure were Belgium and Hungary.

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

II. QUALITY ASPECTS

II.1 Introduction

Ciprofloxacine Altan is a clear and colourless solution for infusion. Each bag with 100 ml of solution for infusion contains 200 mg of ciprofloxacin (as ciprofloxacin lactate). Each bag with 200 ml of solution for infusion contains 400 mg of ciprofloxacin (as ciprofloxacin lactate).

The solution for infusion is packed in flexible bags of both PVC and non-PVC containing 100 ml and 200 ml of solution for infusion.

The excipients are glucose monohydrate, lactic acid, hydrochloric acid and water for injection.

II.2 Drug Substance

The active substance is ciprofloxacin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ciprofloxacin is an almost white or phale yellow, crystalline powder and slightly hygroscopic. The active substance is practically insoluble in water and very slightly soluble in anhydrous ethanol and in methylene chloride.

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. supplemented by a test for residual sovents. Batch analytical data demonstrating compliance with this specification have been provided for 6 commercial scale batches.

Stability of drug substance
The active substance is stable for 5 years 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 development focussed on the possible extractables from the infusion bags and the sterilisation process. It was shown that extractables are not an issue for this product. Since the drug product is a solution for infusion, no bioequivalence studies were performed..

Manufacturing process
The manufacturing process consists of dissolving and mixing the ingredients and filling into the bags. The bags are terminally sterilised by means of autoclaving. The process has been validated according to relevant European guidelines and is described in sufficient detail. Process validation data on the product have been presented for 24 commercial scale batches (including 6 full scale batches), where at least data for three batches of each volume and each infusion bag type, were provided in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph. Eur. requirements, except for (S)-lactic acid. The used lactic acid contains more water that the lactic acid described in the Ph. Eur., and as a result the assay is lower, however, the remainder of the specification is according to the Ph. Eur. The specifications are acceptable.

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, colour, identification,

osmolality, pH, 5-hydroxymethylfurfural, assay of ciprofloxacin, lactic acid and glucose content, related substances, sterility, bacterial endotoxins, sub-visible particles, extractable volume, loss of mass, heavy metals and DHEP content. The latter three are tested at the end of shelf-life only. The release and shelf-life specifications differ with regard to the acceptance criteria for osmolality, 5-hydroxymethylfurfural, pH, the assay values, and the extractable volume, due to the fact that the drug product is packed in semi-permeable containers that might loose water upon storage. The proposed drug product specification is acceptable with regard to the release and shelf-life limits. Satisfactory validation data for the analytical methods have been provided. Batch analytical data 18 commercial 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 18 commercial scale batches stored at 25°C/40% RH (18 and 24 months), 30°C/65% RH (12 months) and 40°C/NMT 25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Three batches of each volume in all three container types were included in the stability studies. No significant changes or trends were observed in the currently available stability data. A photostability test showed that the product is sensitive to light.
Based on the provided stability data, the proposed shelf life of 18 months when stored below 30°C can be granted, with the additional storage conditions “Do not freeze. Protect from light. Store in the original package. Discard if you see alterations on the packaging or in the liquid contained therein.”

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 Ciprofloxacine Altan 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 Ciprofloxacine Altan 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 Ciprofloxacino Anages 2 mg/ml solution for infusion which is available on the European market. 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

Ciprofloxacin 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

Ciprofloxacine Altan 2 mg/ml, solution for 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 Ciprofloxacine Altan 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 Ciprofloxacine Altan.

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

Important identified risks	- Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions - Hepatic necrosis and life-threatening hepatic failure - Tendinitis and tendon rupture

	- Arthropathy in children and adolescents - Exacerbation of symptoms of myasthenia gravis - Seizures - Polyneuropathy - Serious vision disorders - QTc interval prolongation - Depression, suicidality, and psychosis - Pancytopenia and bone marrow depression - Heamolytic disorders especially in patients with glucose-6-phosphate dehydrogenase deficiency - Serious skin disorders (including Erythema multiforme, Stevens- Johnson syndrome, Toxic epidermal Necrolysis & Acute Generalised Exanthematous Pustulosis) - Hypoglycemia - drug-drug interactions especially due to inhibition of CYP1A2
Important potential risks	- Articular cartilage damage following exposure during pregnancy and lactation - Retinal detachment - Selection of drug resistant isolates
Missing information	- Use in children of 1-5 years of age with broncho-pulmonary infections in cystic fibrosis - Use in patients in post-surgical intra-abdominal infections - Use in patients with Inhalational anthrax - Use in children with impaired renal and/or hepatic function

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 Ciprofloxacino Anages. No new clinical studies were conducted. 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 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. 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

Ciprofloxacine Altan 2 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Ciprofloxacino Anages 2 mg/ml solution for infusion. Ciprofloxacino Anages 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 Ciprofloxacine Altan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 February 2019.

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