COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Metronidazol Noridem 5 mg/ml, solution for infusion

(metronidazole)

NL/H/3896/001/DC

Date: 28 March 2019

This module reflects the scientific discussion for the approval of Metronidazol Noridem 5 mg/ml, solution for infusion. The procedure was finalised at 9 October 2018. 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 Metronidazol Noridem 5 mg/ml, solution for infusion, from Noridem Enterprises Ltd.

The product is indicated for infusion in adults and children for the prophylaxis and treatment of infections in which susceptible anaerobic microorganisms have been identified or are suspected to be the cause.

- The prophylaxis of post-operative infections where anaerobic bacteria are expected to be causative pathogens (gynaecologic and intra-abdominal operations)
- The treatment of peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, and post-operative wound infections from which pathogenic anaerobes have been isolated.

Treatment of patients with bacteraemia that occurs in association with any of the infections listed above.

In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazol Noridem.

A prophylactic use is always indicated prior to operations with a high risk of anaerobic infections (gynaecologic and intra-abdominal operations).

- Severe intestinal and hepatic amoebiasis

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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Flagyl 500 mg/100 mg solution for infusion which has been registered in Belgium (license no. BE125054) by Sanofi-Aventis since 30 November 1983 (original product). In the Netherlands reference is made to European Reference Product (ERP) Flagyl 0,5 pour cent, solution injectable pour perfusion en poche, registered in France by Sanofi Aventis France.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Croatia, Czech Republic, France, Hungary, Luxembourg, 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

Metronidazol Noridem is a clear, free of visible particles, almost colourless to pale yellow solution for infusion. 100 mL of solution for infusion contain 500 mg of metronidazole. Each mL of solution for infusion contains 5 mg metronidazole.

The solution for infusion is packed in blow-fill-sealed 100 ml polypropylene bottle over sealed with a moulded plastic cap with a rubber gasket and a pull ring.

The excipients are disodium phosphate dodecahydrate, citric acid monohydrate, sodium chloride and water for injections.

II.2 Drug Substance

The active substance is metronidazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Metronidazole is a white or yellowish, crystalline powder and slightly soluble in water, acetone, alcohol 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. The specification meets the requirements of the monograph in the Ph.Eur. with a tighter limit for any impurity and test and limit for ethylene oxide in line with the CEP as well as additional requirements for microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 4 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 main development studies concerned the characterisation of the reference product and the development of the manufacturing process. The absence of bioequivalence studies versus the reference product is justified in accordance with the Guideline on the investigation of bioequivalence. In general, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps in the manufacturing process are the preparation of the bulk solution and filling. The product is terminally sterilised. The process further includes several bioburden reducing sterile filtration and pre-filtration steps. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled batches and one full scaled batch. The product is manufactured using conventional manufacturing techniques. Additional process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph. Eur. requirements. These 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 of solution, identification, pH, extractable volume, osmolality, assay, related substances, nitrites particulate contamination sterility, bacterial endotoxins and loss of weight. Except for related substances and nitrites, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data one full scaled and two pilot 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 two full scaled batch and two pilot scaled batches stored at 25°C/40% RH (up to 18 months) and 40°C/≤25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline for semi-permeable containers. The batches were stored in the packaging intended for marketing. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The claimed shelf-life of 30 months

and storage condition '*This medicinal product does not require any special storage conditions'* are acceptable.

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 Metronidazol Noridem 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 Metronidazol Noridem 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 Flagyl 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

Metronidazole 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

Metronidazol Noridem 5 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 Metronidazol Noridem 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 Metronidazol Noridem.

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

Important identified risks	• Hypersensitivity (e.g. anaphylaxis, angioedema, severe skin reactions) • Disulfiram-like effect • Pseudomembranous colitis • Bone marrow depression and haematopoiesis • Convulsive seizures, myoclonus and peripheral neuropathy • Use in patients with active or chronic severe peripheral and central nervous system diseases • Hepatic impairment • QT interval prolongation/torsade de pointes in coadministration with amiodarone
Important potential risks	• Overgrowth of non-susceptible organisms • Mutagenic and tumorigenic activity in long term therapy • Increased rate of malformations during use in 1st trimester pregnancy • Secretion into breast milk
Missing information	• Use in patients with renal insufficiency • Use in elderly

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 Flagyl. 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 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

Metronidazol Noridem 5 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Flagyl 500 mg/100 mg solution for infusion. Flagyl 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 Metronidazol Noridem with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 October 2018.

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