COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ivermectine Xiromed 3 mg tablets

(ivermectin)

NL/H/4914/001/DC

Date: 8 July 2021

This module reflects the scientific discussion for the approval of Ivermectine Xiromed 3 mg tablets. The procedure was finalised at 11 February 2021. 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 Ivermectine Xiromed 3 mg tablets, from Medical Valley Invest AB.

The product is indicated for:

- Treatment of gastrointestinal strongyloidiasis (anguillulosis).
- Treatment of suspected or diagnosed microfilaraemia in patients with lymphatic filariasis due to *Wuchereria bancrofti*.
- Treatment of human sarcoptic scabies. Treatment is justified when the diagnosis of scabies has been established clinically and/or by parasitological examination. Without formal diagnosis treatment is not justified in case of pruritus.

Official guidelines should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.

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 Stromectol 3 mg, tablets (NL RVG 28341) which has been registered in The Netherlands by Merck Sharp & Dohme B.V. since 24 March 2003 by the procedure (FR/H/0216/001).

The concerned member states (CMS) involved in this procedure were France and Germany.

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

Repeat use procedure

A repeat use procedure was used to register the product in Austria, Czech Republic, Denmark, Finland, Iceland, Norway, Poland, Sweden and the Slovak Republic.

II. QUALITY ASPECTS

II.1 Introduction

Ivermectine Xiromed is a round, white tablet with no marks and contains 3 mg ivermectin.

The tablets are packed in aluminium/aluminium blisters or HDPE bottles with silica gel dessicant.

The excipients are microcrystalline cellulose, pregelatinised maize starch, citric acid, butylhydroxyanisole and magnesium stearate.

II.2 Drug Substance

The active substance is ivermectin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ivermectin is white to yellowish white crystalline powder and is practically insoluble in water, freely soluble in methylene chloride and soluble in ethanol. Polymorphism has not been observed for Ivermectin. Ivermectin which has 19 and 18 chiral centres respectively. The suitable stereoisomer is generated during the manufacturing process and the chiral purity of Ivermectin is controlled by the routinely performed specific optical rotation test.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The active substance is prepared in three steps. Step one consists of fermentation by a producer microorganism, followed by extraction and purification. The following steps consist of dissolving, purifying, drying and sieving. The final batches may be milled to get the required particle size. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

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 ASMF. Both the MAH and ASMF holder provided additional acceptance criteria for identified impurities, and any other unknown impurity using the validated Ph.Eur. method with some slight modifications. The MAH also provided additional acceptance criteria for particle size distribution. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for two scale batches.

Stability of drug substance

Stability data on the active substance have been provided for six standard scale batches, three standard (non-milled) and three milled batches stored at 5˚C ± 3˚C (up to nine months) and 25°C/60% RH (six months). The proposed retest period of 12 months for the active drug substance stored in a refrigerator at 5˚C is justified as no clear trends or significant changes were observed for any of the tested parameters.

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. Compatibility of the excipients with the drug substance was demonstrated. The pharmaceutical development is based on the similarity with reference product Stromectol.

A bioequivalence study has been performed. Comparative dissolution studies between the proposed drug product and the reference product were performed and show essential similarity with respect to the major physicochemical parameters. The flow properties of the drug substance are poor but this was solved by formulation optimisation studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The process consists of: mixing, sieving, lubrication, final blending, compression and packaging. Process validation data on the product have been presented for three batches of pilot scale in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. requirements. For cellulose microcrystalline, magnesium stearate and pregelatinised starch a validated particle size distribution test is added. For magnesium stearate the specific surface area test is performed and for pregelatinised starch the cold water soluble matter test is performed. 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, identity, uniformity of dosage units, assay, water content, dissolution, related substances, antioxidant content and microbial control. The release and shelf life acceptance criteria are equal for all parameters except for the antioxidant content. 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 from three pilot 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 pilot scale batches for each primary packaging (alu/alu blisters and HDPE bottles) stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. There were no clear positive or negative trends for the tested parameters in any of the tested batches, except for the antioxidant content which clearly

decreased. However, based on the trends during 24 months long term storage, no out of specification results are expected after 36 months of storage.
The photostability study is included in the stability data and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are: 'This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect the product from light'.
Stability data have been provided demonstrating that the product remains stable for 83 days following first opening of the container when stored at 25°C/60% RH. As the results of the in-use study demonstrate that there is no impact on the stability of the drug product by frequent opening of the HDPE bottles, no in-use claim is applicable in the SmPC.

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 Ivermectine Xiromed 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 Ivermectine Xiromed 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 Stromectol 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

Ivermectin 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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivermectine Xiromed 3 mg tablets (Medical Valley Invest AB, Sweden) is compared with the pharmacokinetic profile of the reference product Stromectol 3 mg, tablets (Merck Sharp & Dohme B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A randomised, open label, two treatment, four period, four sequence, single dose, fully-replicate design, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male and female subjects, aged 20-45 years. Each subject received a single dose (3 mg) of one of the 2 ivermectin formulations. The tablet was orally administered with 240 ml water after overnight fast of at least 10 hours. There were 4 dosing periods with a wash-out period of 28 days.

Blood samples were collected at pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 3.75, 4.0, 4.25, 4.5, 4.75, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 18.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets should be taken without food. As such, the fasting conditions applied in the study is considered adequate.

The ivermectin B1a, B1b analytes and total ivermectin were taking into account. Results for ivermectin B1b and total ivermectin were considered as supportive.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Five subjects withdrew from the study on their own accord and one subjects was withdrawn due to administrative reasons. Therefore, a total of 42 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ivermectin B1a under fasted conditions.

Treatment N=42	**AUC_{0-72h} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	188 ± 68	14.0 ± 4.9	4.0 (2.0 – 10.0)
Reference	196 ± 85	14.7 ± 6.4	4.0 (2.0 – 10.0)
***Ratio (90% CI)**	0.99 (0.92 – 1.06)	1.01 (0.92 – 1.10)	--
CV (%)	34.0	44.3	--

AUC_{0-72h} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ivermectine Xiromed is considered bioequivalent with Stromectol.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Ivermectine Xiromed.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity reactions - Encephalopathy following treatment in patients with heavy Loa loa co-infection
Important potential risks	- Lack of efficacy in immunocompromised patients
Missing information	- Use in lactation - Drug interaction

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 Stromectol. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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

Ivermectine Xiromed 3 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Stromectol 3 mg, tablets. Stromectol is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Ivermectine Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 February 2021.

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/4914/001/E/001	A repeat use procedure	-	17-06-2021	Approved	-