COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ivermectine Sigillata 3 mg tablets (ivermectin)

NL/H/3678/001/DC

Date: 31 May 2022

This module reflects the scientific discussion for the approval of Ivermectine Sigillata 3 mg tablets. The procedure was finalised on 26 January 2022. 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 Sigillata 3 mg tablets, from Sigillata Limited.

The product is indicated for:

- Treatment of intestinal strongyloidiasis (anguillulosis).
- Treatment of proven or suspected microfilaremia in patients with lymphatic filariasis caused by *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.

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 France by MSD since 1999 (original product). In the Netherlands, Stromectol has been registered since 2003 by the procedure FR/H/216/001/MR.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Ivermectine Sigillata is an uncoated, round tablet, white marked with “A 300” on one side, and contains as active substance 3 mg of ivermectin.

The tablets are packed in aluminium unit strips and boxes.

The excipients are micro crystallised cellulose (E460), pregelatinised corn starch, butylhydroxyanisole (E320), citric acid -anhydrous (E330) and magnesium stearate (E572).

II.2 Drug Substance

The active substance is ivermectin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or yellow white, slightly hygroscopic, crystalline powder and is practically insoluble in water, freely soluble in methylene chloride

and soluble in ethanol (96%). Ivermectin is classified as a BCS class IV drug because of its very limited solubility in water and low permeability. Ivermectin is consistently produced in its anhydrous form.

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 is in line with the CEP with no additional requirements. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for three years when stored in a polyethylene bag in a tin. 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 development of the product has been described, the choice of excipients is justified and their functions explained. Tablets made by compression and two granulation steps gave satisfactory tablets. The compression was tested on and the granulated batch gave the best overall results. The granulation method was chosen as manufacturing method for Ivermectin tablets. Furthermore, the amount of anti-oxidant was optimized and a bioequivalence study between test and reference product demonstrated that the batches were bioequivalent. A dissolution method was developed and the discriminatory capabilities were demonstrated.

The pharmaceutical development of the product overall has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process consists of granulation followed by drying and tablet compression.

Process validation data on the product have been presented for three production-scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
All excipients used for manufacture of Ivermectin tablets are described and controlled according to the European Pharmacopoeial monograph. 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, average weight, uniformity of dosage units, disintegration, assay of ivermectin and of butylhydroxyanisole, related substances dissolution and microbiology. 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 five production 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 five production-scaled batches stored at 25°C/60% RH (up to 24 months) or 30°/75% RH (up to 12 months) and 40°C/75% RH (up to six months) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. All parameters remained within the specification limits. No out-of-specification results are observed. A photostability study has been performed in line with the Note for guidance on the photostability testing of new active substances and medicinal products demonstrating that the drug product should be protected from light. On basis of the data submitted, a shelf life was granted of 24 months when stored in the original container in order to protect from light. An adequate risk-assessment on the subject of nitrosamines has been performed, no potential risks were identified.

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 Sigillata 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 Sigillata 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ivermectin 3 mg tablets (Actavis, Malta) is compared with the pharmacokinetic profile of the reference product Stromectol 3 mg tablets (MSD, France). As the active substance ivermectin can be found in two forms (B1a and B1b) and both forms can be found in the drug product, the MAH has provided data for both of these forms. It should be noted that the B1a form is the major component (>90% of the active substance content) and the B1b form is only present in small amounts.

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

Bioequivalence studies

Design

A open labelled, randomized, single dose, two way crossover bioequivalence study was carried out under fasted conditions in 62 healthy male subjects, aged 18-42 years. Each subject received a single dose (6 mg, two times 3 mg tablet) of the two ivermectin formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 11 days.

Blood samples were collected at pre-dose and at 0.5, 1.0, 2.0, 2.5, 3.25, 3.5, 3.75, 4.0, 4.25, 4.5, 4.75, 5.0, 5.5, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable.

According to the SmPC, the tablets should be taken without food. As such, the fasting conditions applied in the study is considered adequate.

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

Out of a total of 62, 52 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn because of adverse events, three subjects did not check in and three subjects were withdrawn because of a positive urine drug screening. Furthermore, one subject tested positive for alcohol breath analysis and finally one subject withdrew his consent.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ivermectin B1a (6 mg) under fasted conditions.

Treatment N=52	**AUC_{0-72h}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	690 ± 208	38.7 ± 11.6	4.25 (2.5 – 6.0)	50 ± 18
Reference	622 ± 212	34.3 ± 12.3	4.25 (3.0 – 8.0)	51 ± 19
***Ratio (90% CI)**	1.11 (1.05 – 1.18)	1.15 (1.07 – 1.23)	--	--
CV (%)	15.8	18.4	--	--

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation
CI	confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ivermectin B1b (6 mg) under fasted conditions.

Treatment N=52	AUC_{0-72h} (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	15860 ± 4532	687 ± 187	4.25 (2.5 – 8.0)	68 ± 34
Reference	11326 ± 2773	482 ± 131	4.50 (2.0 – 8.0)	61 ± 25
***Ratio (90% CI)**	1.36 (1.29 – 1.44)	1.42 (1.34 – 1.51)	--	--
CV (%)	14.1	14.8	--	--

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation
CI	confidence interval

**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 for the B1a form. Bioequivalence was not proven for the B1b form. However, because of the low contents of this analyte and the data that the MAH has provided for potency and dose normalised AUC and C_{max}, the bioequivalence of the drug product was considered to be adequate. Based on the submitted bioequivalence study Ivermectine Sigillata 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 Sigillata.

Table 3. 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 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

Ivermectine Sigillata 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ivermectine Sigillata with the reference product, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 26 January 2022.

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