COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ivergalen 3 mg, tablets

(ivermectin)

NL/H/5040/001/DC

Date: 22 January 2021

This module reflects the scientific discussion for the approval of Ivergalen 3 mg, tablets. The procedure was finalised on 5 November 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
EDQM	European Directorate for the Quality of Medicines
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 Ivergalen 3 mg, tablets from Galenicum Derma, S.L.

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 Licence RVG 28341) which has been registered in Netherlands by Merck Sharp & Dohme B.V. since 24 March 2003 through mutual recognition procedure FR/H/0216/001.

The concerned member state (CMS) involved in this procedure was Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Ivergalen 3 mg is a round, white or almost white, flat chamfered tablet.

The tablets are packed in aluminium/aluminium blisters.

The excipients are: microcrystalline cellulose (E 460), pregelatinised maize starch, butylhydroxyanisole (E 320) and magnesium stearate (E 470b).

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. The drug substance produced by both manufacturers exists in a unique crystalline form and does not show polymorphism.

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

The manufacturing process includes the manufacturing of a non-micronised variant of the active substance. Since a CEP has been submitted; no details on this process have been included. Subsequently, the particle sizes of the non-micronisation active substance are reduced in a micronisation chamber. The second part of the manufacturing process has been adequately described.

Quality control of drug substance

The non-micronised and micronised active substances comply with the Ph. Eur. Only for the non-micronised ivermectin additional tests and limits for the impurities and residual solvents are included on the CEP. Batch analytical data demonstrating compliance with the Ph. Eur. monograph of the active substance and the additional tests per CEP have been provided for three batches.

Stability of drug substance

The non-micronised active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Stability data on the micronised active substance have been provided for one batch stored for three months under warehouse conditions. Due to changes in the related substances and impurities, the active substance should be used within one month after micronisation.

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 choices of the packaging and manufacturing process are justified in relation to the innovator. A bioequivalence study was performed between the test product Ivergalen 3 mg tablets and the reference product Stromectol 3 mg, tablets. The manufacture and composition of the biobatch used in the bioequivalence studies was similar to the proposed marketed product. The dissolution method used for routine dissolution was shown to be discriminatory.

Manufacturing process

The product is manufactured in eight steps using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three industrial-scale batches.

Control of excipients

The excipients comply with 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, resistance to crushing, disintegration, average mass, identification and assay of the active substance and the antioxidant, uniformity of dosage units of the active substance, assay of the degradation products, dissolution and microbiological quality. 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 industrial scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.
A nitrosamine risk evaluation has been adequately performed. A low risk for nitrosamines has been identified. Confirmatory testing analyses have shown that there is no risk of its presence on the final product.

Stability of drug product

Stability data on the product have been provided for four industrial-scale batches 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. The batches were stored in the intended blisters. Photostability studies were not performed, as pharmaceutical development indicated that that the product is not stable when exposed to light. At 40°C/75% RH a decrease in the assay values of the drug substance is observed with time. At both 25°C/60% RH and 40°C/75% RH, several changes in the impurity profile are noticed mainly in the unknown impurities. No specific increase is seen in a specific impurity since the results fluctuate. Overall the amount of total impurities increases over time. All values remain within the qualified Ph.Eur. limits that are applicable for the drug substance. Stability data of one batch stored at the intermediate condition of 30°C/65% RH is available. This batch showed an out of specification result for total impurities. Therefore, the additional storage condition of “Do not store above 25°C” is justified. Generating more data of batches stored at 30°C/65% RH will be of no additional value.

On the basis of the provided stability data the claimed storage period of 18 months, 'do not store above 25°C', can be granted.

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 Ivergalen 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 Ivergalen 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 conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivergalen 3 mg (Galenicum Derma, S.L., Spain) is compared with the pharmacokinetic profile of the reference product Stromectol 3 mg, tablets (Merck Sharp & Dohme B.V., NL).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy (17 males and 19 females) subjects, aged 25-71 years. Each subject received a single dose (9 mg; 3x3 mg tablet) of one of the 2 ivermectin formulations. The tablets were orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 2.33, 2.67, 3, 3.33, 3.67, 4.0, 4.33, 4.67, 5.0, 5.33, 5.67, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 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.

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

One subject withdrew consent before dosing of the second period. Therefore, 35 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 under fasted conditions.

Treatment N=35	**AUC_{0-72h}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$**
Test	525 ± 142	36.7 ± 12.3	3.67 (2.0 – 8.0)	51 ± 24
Reference	544 ± 177	37.5 ± 14.7	4.33 (2.0 – 7.0)	53 ± 23
***Ratio (90% CI)**	0.99 (0.90 – 1.08)	0.99 (0.88 – 1.13)	--	--
CV (%)	22.4	32.0	--	--

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
$t_{1/2}$ half-life
CV coefficient of variation

**In-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 Ivergalen 3 mg tablets is considered bioequivalent with Stromectol 3 mg, tablets.

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 Ivergalen.

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 interactions

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 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 package leaflet 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

Ivergalen 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 state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ivergalen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 November 2020.

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