

Public Assessment Report

Scientific discussion

Ivermectine Aristo 3 mg and 6 mg, tablets (ivermectin)

NL/H/6235/001-002/DC

Date: 6 July 2026

This module reflects the scientific discussion for the approval of Ivermectine Aristo 3 mg and 6 mg, tablets. The procedure was finalised on 18 November 2025. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Aristo 3 mg and 6 mg, tablets, from Aristo Pharma GmbH.

The product is indicated for the:

- treatment of gastrointestinal strongyloidiasis (anguillulosis);
- treatment of diagnosed or suspected 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC for the 3 mg strength and to Article 10(3) for the 6 mg strength. The 3 mg strength concerns a generic application, the 6 mg strength concerns a hybrid application due to the additional strength compared to the reference product.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Stromectol 3 mg, tablets, which has been registered in France by Merck Sharp & Dohme BV via decentralised procedure FR/H/0216/001 since 1999.

The concerned member states (CMS) involved in this procedure were Czechia, Germany, Poland (only for the 3 mg strength) and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Ivermectine Aristo is a tablet. Each tablet contains as active substance 3 mg or 6 mg of ivermectin, depending of the strength. The two strengths can be distinguished by size and break mark, as follows:

Ivermectine Aristo 3 mg

The tablets are white to off white coloured, round shaped and biconvex having a diameter of approximately 5 mm.

Ivermectine Aristo 6 mg

The tablets are white to off white coloured, round shaped, biconvex tablets with a break mark having a diameter of approximately 6 mm. The tablet can be divided into equal doses.

The excipients are microcrystalline cellulose (E460), citric acid (E330), butylhydroxyanisole (E320), pregelatinised starch, colloidal anhydrous silica (E551) and magnesium stearate (E470b).

The two tablet strengths are dose proportional.

The tablets are packed in blister cards consisting of oriented polyamide/aluminium/polyvinyl chloride (OPA/Alu/PVC) foil sealed with a heat seal lacquered aluminium foil.

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 crystalline powder and practically insoluble in water. No polymorphism is reported for ivermectin in the literature.

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

Two CEPs have been submitted. Therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the CEP, with additional requirements for particle size distribution. The specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for one batch per manufacturer.

Stability of drug substance

Stability data on the active substance have been provided by manufacturer 1 for five full scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of six months when stored under the stated conditions.

The active substance supplied by manufacturer 2 is stable for three 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 are explained. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by slugging, whereby a blend of excipients and active substance is compressed, milled, blended with magnesium stearate and finally compressed into tablets. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per strength, in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

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, identity, assay ivermectin and one specific anti-oxidant, dissolution, related substances, microbial purity and uniformity of dosage units. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided, demonstrating that the risk for nitrosamine impurity formation is low and stating that no additional control measures are required. This is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from six batches (three per strength) 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 six batches stored at 25°C/60% RH (24 months), 30°C/65% RH (up to 12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: *"Do not store above 25°C. Store in the original package in order to protect the product from light."*

The MAH made a post approval commitment on the storage conditions, see section II.4.

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 Aristo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- **Quality part:** the MAH committed to test the dissolution of the drug product under intermediate conditions and, eventually, under accelerated conditions. Required changes to the medicinal product information based on the new data should be requested via variations.
- **Non-clinical part/ environmental risk assessment (ERA):** The MAH committed to provide relevant and reliable data for the adsorption of ivermectin to sludge, using a batch equilibrium method with 2 sludges (OECD 106) as a joint study within the programme of the EMA according to Article 23 of the Draft Directive 2023/0132. Participation of the MAH will be according to the expected contribution of products of the MAH to the overall environmental exposure of ivermectin. The following aspects should be re-evaluate and reported in the updated ERA:
 - triggering and characterisation of risks for groundwater via bank filtration
 - triggering and calculations of the soil risk assessment
 - triggering and characterisation of risks for groundwater via pore water

The MAH is requested to provide a new and complete ERA taking into account all requested additions and adjustments. Required changes to the medicinal product information based on the new ERA should be requested via variations.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of ivermectin are well known. As ivermectin is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. An overview based on literature is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

This (generic) application was submitted before the new guideline that requires an ERA for all generic pharmaceuticals was effective (EMA/CHMP/SWP/4447/00 Rev. 1; September 1, 2024). The MAH provided an ERA, which was considered not acceptable yet at the end of the procedure. Therefore, the MAH made a post approval commitment on the ERA, see section II.4.

III.3 Discussion on the non-clinical aspects

This product is a generic/hybrid formulation of Stromectol which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 besides the bioequivalence study, which is discussed below. In addition, a biowaiver of strengths is requested.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivermectine Aristo 6 mg, tablets (Aristo Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Stromectol 3 mg, tablets (Merck Sharp & Dohme, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results (at pH 0.1, 4.5 and 6.8) and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for the additional 3 mg strength is claimed, according to the EMA Bioequivalence guideline:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,

- c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths,
- d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing. The dissolution profile between Ivermectin Aristo 6 mg tablet and 2 tablets Stromectol 3 mg tablets and in between Ivermectin Aristo 3 mg tablets and Ivermectin Aristo 6 mg tablets (both test strengths), are the same.
- e. the pharmacokinetic profile of ivermectin is linear. Ivermectin exhibits linear pharmacokinetics over the dose range of 6-15 mg. At low doses, the $C_{\max}$ is proportional to the dose, but this proportionality is lost with doses equal or higher than 150 µg/kg.

All requirements have been met.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor value at pH 6.8 was within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. At pH 0.1 and 4.5, the dissolution values in media without surfactant were zero. This is in line with Ph.Eur. monograph for ivermectin, which states it is practically insoluble in water. These profiles are considered similar.

The biowaiver for the 3 mg additional strength is justified.

Bioequivalence studies

Design Study 008B23

A single-dose, randomised, open label, four-period, two-treatment, two-sequence, crossover replicate design bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-53 years. Each subject received a single dose (6 mg) of one of the two ivermectin formulations. One tablet of 6 mg was/two tablets of 6 mg were orally administered with 240 ml water after an overnight fasting for at least 10 hours. There were four dosing periods, separated by a washout period of at least 28 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

ivermectin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ivermectin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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 discontinued the study: one of them was withdrawn after period 1 due to an adverse event, another after period 2 due to a serious adverse event (not related to investigational products). Three other subjects were withdrawn for personal reasons, two after period I and one after period II. In total, 37 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=37	AUC ₀₋₇₂ (ng.h/mL)	C _{max} (ng/mL)	t _{max} (h)
Test	388 $\pm$ 152	23 $\pm$ 9	4.00 (2.00 – 8.00)
Reference	370 $\pm$ 171	23 $\pm$ 9	4.00 (2.00 – 6.00)
*Ratio (90% CI)	1.08 (0.99 – 1.17)	1.01 (0.94 – 1.10)	--
AUC_{0-∞} Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / t=72 hours C_{max} Maximum plasma concentration t_{max} Time after administration when maximum plasma concentration occurs CI Confidence interval			

**In-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC₀₋₇₂ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ivermectine Aristo 6 mg is considered bioequivalent with Stromectol 2x3 mg tablets.

The results of study 008B23 with the 6 mg formulation can be extrapolated to the 3 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Aristo. At the time of approval, the most recent version of the RMP was version 0.2 date of final sign off 11 April 2025.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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. The MAH demonstrated through a bioequivalence study and a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic (3 mg strength) and hybrid (6 mg strength) medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

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 three 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 Aristo 3 mg and 6 mg, tablets have a proven chemical-pharmaceutical quality and are generic (3 mg strength) or hybrid (6 mg strength) forms 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 Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 November 2025.

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
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.