COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Levonorgestrel Aristo 1.5 mg tablets (levonorgestrel)

NL/H/5655/001/DC

Date: 22 July 2026

This module reflects the scientific discussion for the approval of Levonorgestrel Aristo mg tablets. The procedure was finalised on 25 October 2023. 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 Levonorgestrel Aristo 1.5 mg tablets, from Aristo Pharma GmbH.

The product is indicated for:
Emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

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, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Postinor 1500 microgram, tablets, which has been registered in Czechia via mutual recognition procedure (CZ/H/0939/001) since 11 January 2007.

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

II. QUALITY ASPECTS

II.1 Introduction

Levonorgestrel Aristo is a white to off white, round bevel edged, flat faced tablet debossed with “J06” on one side and plain on other side. Each tablet contains 1.5 mg levonorgestrel as active substance.

The excipients are: maize starch, potato starch, talc (E 553b), colloidal anhydrous silica (E 551), magnesium stearate (E 470b) and lactose monohydrate.

The tablets are packed in a clear and transparent polyvinyl chloride(PVC)/Aluminium blister.

II.2 Drug Substance

The active substance is levonorgestrel, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white o off white crystalline powder and is practically insoluble in water.

Two CEP procedures are 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
CEPs have 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 meets the requirements of the monograph in the Ph.Eur. and the CEPs. Batch analytical data demonstrating compliance with this specification have been provided for seven commercial scale batches.

Stability of drug substance
CEP holder 1
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

CEP holder 2
The stability of drug substance has been evaluated within the scope of the CEP procedure by the EDQM. The re-test period of levonorgestrel is 12 months when stored under the stated conditions.

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. All excipients used are well known. Formulation development and manufacturing process development have been adequately described.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two full scaled batches in accordance with the relevant European guidelines.

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 description, identification, average weight, weight variation, friability, disintegration time, water content, dissolution, uniformity of dosage units, assay, related substances and microbiological tests. 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. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from nine full scaled batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from nine full scaled batches stored at 25°C/60% RH (36 or 24 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 48 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for each excipient have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

There are no substances of ruminant animal origin 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 Levonorgestrel Aristo 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 Levonorgestrel Aristo is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Postinor 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

Levonorgestrel is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the 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 Levonorgestrel Aristo 1.5 mg tablets (Aristo Pharma GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Levonelle 1500 microgram tablets (Medimpex UK Limited, United Kingdom).

The bioequivalence study took place in 2016, i.e. when the United Kingdom was still a EU member state. At the time, the reference product used in the bioequivalence study belonged to the same mutual recognition procedure as the reference product Postinor 1500 microgram, tablets (Gedeon Richter Plc, Hungary). Therefore it can be concluded that the products are identical.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

<u>Bioequivalence studies</u>

Design

A single-dose, open label, balanced, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy female subjects, aged 26-44 years. After a fasting period of at least 10 hours, each subject received a single dose (1.5 mg) of one of the two lenorgestrel formulations. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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
Two subjects were withdrawn from the study due to adverse events (human chorionic gonadotropin increased), one subject had a pre-dose concentration value > 5% of C_{max} in Period-I & II and hence same, was excluded from the pharmacokinetic analysis. The other 37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of levonorgestrel, 1.5 mg under fasted conditions.

Treatment N=37	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	283 ± 126	-	17 ± 6	2.25 (1.00 – 5.00)
Reference	288 ± 130	-	18 ± 7	2.00 (1.25 – 5.00)
***Ratio (90% CI)**	0.93 (0.88 – 0.98)	-	0.99 (0.93 – 1.04)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Levonorgestrel Aristo 1.5 mg is considered bioequivalent with Levonelle 1500 microgram, and therefore bioequivalent to Postinor 1500 microgram.

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 Levonorgestrel Aristo. At the time of approval, the most recent version of the RMP was version 0.2 dated 13 March 2023.

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 Postinor. 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 4 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

Levonorgestrel Aristo 1.5 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Postinor 1500 microgram, tablets. Postinor 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 Levonorgestrel Aristo with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 2023.

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/5655/001 /IA/003/G	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process. Change to in-process tests or limits applied during the manufacture of the finished product - Other variation Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	No No No	26-5-2025	Approved	N/A
NL/H/5655/001 /IB/002/G	Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use - Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location Change in the (invented) name of the medicinal	No Yes	19-6-2025	Approved	N/A

	product - for Nationally Authorised products				
NL/H/5655/001/IB/004	Change in the (invented) name of the medicinal product - for Nationally Authorised products	Yes	4-11-2025	Approved	N/A
NL/H/5655/IA/006/G	Change in the manufacturing site for part or all of the manufacturing process of the finished product (except for batch release and batch control testing sites) - Addition or replacement of a site responsible for secondary packaging Change to batch release arrangements and batch control testing of the finished product - Addition or replacement of a site responsible for batch release (QP certification) - Not including batch control/testing	No Yes	9-4-2026	Approved	N/A
NL/H/5655/001/IA/005	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: — for an active substance — for a starting material/reagent/intermediate used in the manufacturing process of the active substance — for an excipient - European Pharmacopoeial	No	16-4-2026	Approved	N/A

	Certificate of Suitability to the relevant Ph. Eur. Monograph - Update of an approved certificate of suitability (CEP)				