COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Clozapine Aristo 25 mg, 50 mg, 100 mg and 200 mg, tablets (clozapine)

NL/H/6394/001-004/DC

Date: 10 April 2025

This module reflects the scientific discussion for the approval of Clozapine Aristo 25 mg, 50 mg, 100 mg and 200 mg, tablets. The procedure was finalised at 26 January 2022 in Germany (DE/H/6879/001-004/DC). After a transfer on 20 February 2025, the current RMS is the Netherlands. 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 data on quality, safety and efficacy, the application for Clozapine Aristo 25 mg, 50 mg, 100 mg and 200 mg, tablets, from Aristo Pharma GmbH is approved.

The product is indicated for:
Treatment-resistant schizophrenia
Clozapine Aristo is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.
Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Psychosis during the course of Parkinson's disease
Clozapine Aristo is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

Safety
Clozapine can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of white blood cell (WBC) counts and absolute neutrophil count (ANC) monitoring.
Precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations (see SmPC for further details).

A comprehensive description of the up-to-date indications and posology is given in the current SmPC.

This Marketing Authorisation Application is based on Article 10(1) of Directive 2001/83/EC, as amended. In compliance with above mentioned Article, Clozapine 25 mg / 50 mg / 100 mg / 200 mg tablets have the same qualitative and quantitative composition of drug substance and the same pharmaceutical form as the reference medicinal product Leponex 25 mg / 50 mg / 100 mg Tabletten and Clozapin Dura 200 mg Tabletten in Germany.
The qualitative composition of the products applied for is the same as that of the reference product Leponex. Although there are minor differences in the qualitative composition of Clozapin Dura 200 mg and the other products these differences seem not to alter the PK profile.

The bioequivalence study was performed with the originator product Leponex 25 mg and a biowaiver for the additional strengths (50 mg, 100 mg, 200 mg) is requested.
As no 200 mg strength of the originator product Leponex is available, the applicant has chosen Clozapin Dura 200 mg tablets from Mylan Dura GmbH, registered since 26 July 2010 (withdrawn on 22 June 2017), as reference product for Clozapine Aristo 200mg tablets. This is acceptable as all four products belong to the same GMA.

The concerned member states (CMS) involved in this procedure were Austria, Czechia, France, Poland, Portugal and Spain.

II. QUALITY ASPECTS

II.1 Drug Substance

Clozapine is described in the current European Pharmacopoeia. One source of Clozapine is proposed. The drug substance manufacturer holds a valid Certificate of Suitability, issued by the EDQM, certifying that the quality of the drug substance is suitably controlled by the current version of the Ph. Eur. monograph of Clozapine. A copy of the valid CEP with filled in declaration of access has been provided.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Stability of drug substance
The re-test period of the substance as stated on the CEP is 5 years if stored in double polyethylene bags placed in either a cardboard or a paperboard drum.

II.2 Medicinal Product

Pharmaceutical development
The development of the products has been described, the choice of excipients is justified and their functions explained.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches of each strength, except for the 100 mg strength, for which batch analysis of two batches has been performed. The batch analysis results show that the finished products meet the specifications proposed. Adequate justification of specifications has been provided and a risk evaluation concerning the presence of Nitrosamine impurities in the products performed

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The proposed shelf-life of 21 months for the drug products with the labelled storage condition “Do not store above 30 °C” has been justified by stability results provided.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Clozapine Aristo 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

Pharmacodynamic, pharmacokinetic and toxicological properties of clozapine are well known. As clozapine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview refers 80 publications up to year 2020.

Based on published pre-clinical pharmacological, toxicological and pharmacokinetic data, the properties of the active substance have been adequately described in the non-clinical overview.

Instructions regarding the use of the active substance during pregnancy and lactation and information on available preclinical safety data contained in the proposed SPC are acceptable. The wording of the PIL concerning non-clinical sections is appropriate. The non-clinical documentation is hence considered sufficient to support the application.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted as report one bioequivalence study.

IV.2 Pharmacokinetics

Biowaiver for additional strengths

A biowaiver for the additional strengths, i.e. 50 mg, 100 mg and 200 mg, can be accepted as all biowaiver requirements are met, according to the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98).

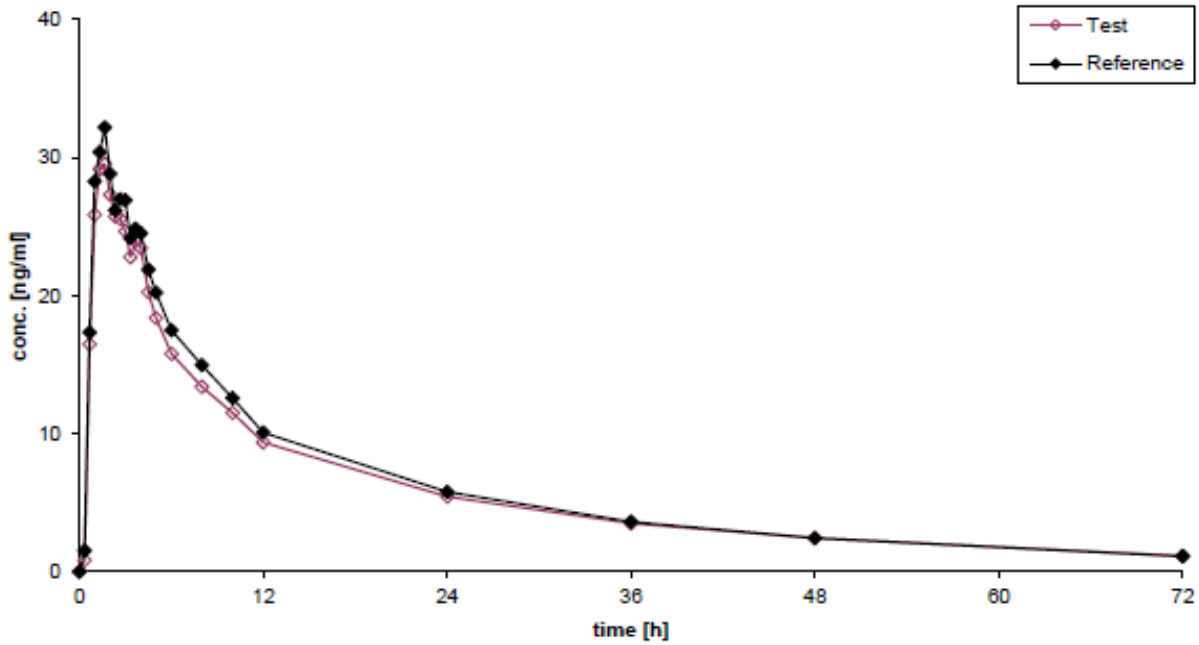
Bioequivalence study

The study was conducted with the lowest possible dose of 12.5 mg clozapine (one half tablet of the lowest dose strength of 25 mg) due to safety/tolerability reasons in healthy volunteers

which is acceptable as per EMA Guideline On The Investigation Of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Jan 2010).

Plasma concentration- time curve
The plasma concentration-time curves of clozapine after administration of the test product and the reference product (in arithmetic mean) is presented in Figure 1.

Figure 1. Mean (Arithmetic Mean) Plasma Concentration-Time Curves of Clozapine after Administration of the Test Product and the Reference Product (N = 24) in Study 052B18:



The arithmetic mean of pharmacokinetic parameters are presented in Table 5.

Table 5. Pharmacokinetic Data for Clozapine in Study 052B18:

Pharmacokinetic parameter	Arithmetic means (±SD)	
	Test product	Reference product
$AUC_{(0-t)}$ [ng/ml*h]	415.9376 (±201.27360)	444.0684 (±159.96971)
$AUC_{(0-\infty)}$ [ng/ml*h]	460.7394 (±245.49020)	478.4992 (±182.03641)
C_{max} [ng/ml]	34.2581 (±13.33764)	36.2635 (±12.89532)
t_{max} [h] (Median, Min, Max)	1.50, 0.66, 4.00	1.33, 0.66, 5.00

Results
Main bioequivalence results are tabulated in Table 7.

Table 7 Bioequivalence Evaluation of Clozapine in Study 052B18:

Pharmacokinetic parameter	Geometric Mean Ratio % T/R	Confidence Intervals %	CV %
$AUC_{(0-t)}$	91.08	82.07 – 101.08	21.25
C_{max}	93.41	83.30 – 104.75	23.43

The results of this study showed that for the extent of absorption i.e. AUC(0-t) and the rate of absorption (Cmax) the 90% CI are within the acceptance range of 80.00 % - 125.00 %.

It can be concluded that for the extent of absorption i.e. AUC(0-t) and the rate of absorption (Cmax) the test product half a tablet of Clozapine 25 mg tablets demonstrated bioequivalence to the reference product half a tablet of Leponex 25 mg Tabletten.

IV.3 Risk Management Plan

The MAA 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 the medicinal product(s) applied for authorisation.

Safety specification
According to the Applicant the safety specification is in full accordance with the current safety specification agreed and published for a similar product/similar products which is acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan is considered acceptable.
After approval the MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or

as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application contains an adequate review of published clinical and non-clinical data.
Based on the submitted bioequivalence study 052B18, half a tablet of Clozapine Aristo 25 mg, 50 mg, 100 mg and 200 mg, tablets by Aristo Pharma GmbH, Germany, is considered bioequivalent with half a tablet of Leponex 25 mg Tabletten by Mylan Healthcare GmbH, Germany.
The results of study 052B18 can be extrapolated to other strengths, i.e. 50 mg, 100 mg and 200 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6. Approval is recommended from the clinical and non-clinical point of view.
From quality point of view the B/R is considered positive and approval can be recommended.
The application is approved. For intermediate amendments see current product information.

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
-	-	-	-	-	-