LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tranylcypromine Afortas
(tranylcypromine sulfate)

SE/H/2693/001/DC

This module reflects the scientific discussion for the approval of Tranylcypromine Afortas. The procedure was finalised at 2026-03-11. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Tranylcypromine Afortas, 10 mg, Film-coated tablet.

The active substance is tranylcypromine, tranylcypromine sulfate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Tranylcypromine is a nonselective and irreversible monoamine oxidase (MAO) inhibitor indicated for treatment resistant depression. It is since long known for unfavourable interactions with a diet rich in tyramine, the "cheese reaction", and with a range of other drugs including SSRI.

II.2 General comments on the submitted dossier

The application for Tranylcypromine Afortas, 10 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Jatrosom, 10mg, filmcoated tablet, authorised in Germany since 1999, with Aristo Pharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Jatrosom, 20 mg, tablets, from DE with Aristo Pharma GmbH as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in RMS and CMS NO: Jatrosom, 10mg, filmcoated tablet authorised in Germany since 1999, with Aristo Pharma GmbH as marketing authorisation holder.

The justification to use this product is based on information received from Germany. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided.

No issues regarding GCP have been identified. The clinical and bioanalytical facilities have recently been inspected without any critical findings.

Hence, no inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of tranylcypromine are well known. As tranylcypromine is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The applicant informs that no previous ERA could be obtained, thus a literature ERA has been provided

PHASE I

PBT/vPvB Screening
A log D value of 0.699 at pH 7.4 has been reported using the shake-flask method (Gulyaeva et al., 2003), and a log Kow value of 1.58 at pH 13 was determined by gas chromatography after partitioning between octanol and 0.1 M sodium hydroxide (Grunewald et al., 1984)

Risk Assessment
PEC sw has been calculated using default fpen. PECSW = 60mg * 0,01 / 200*10 =0,0003 mg/L =0,3µg/L

This triggers phase II tier A

PHASE II

Tranylcypromine's environmental fate, and parts of ecotoxicity, is estimated from studies on analogous compounds, such as methamphetamine and amphetamine, due to a lack of direct data. No sediment data has been provided.

Discussion and overall conclusion
Phase I
Hazard: A log D of 0.699 at pH 7.4 and a log Kow of 1.58 at pH 13 have been reported. These values are considered acceptable, and no further PBT assessment is required.

Risk: Access to previous ERAs was denied. PECsw has been calculated using Fpen default, which is acceptable. The result triggers a phase II ERA.

Phase II:
The applicant has not provided i Phase II assessment in line with the current guidlines. Unacceptable analogues have been used instead of the actual substance, and there is a complete lack of data for the sediment compartment. Thus, no conclusion on environmental impact can be done at this time.

The applicant has provided a letter of commitment stating that a new ERA will be provided within 5 years. This is acceptable.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant had initially conducted one bioequivalence study comparing Tranylcypromine 20 mg tablets with the reference product Jatrosom, 20 mg tablets. However, only 10 mg was applied.

In order to support the BE study conducted with the higher strength, the applicant was asked to submit literature references supporting that tranylcypromine is linear or shows more than proportional increases in AUC and/or C_{max} with increasing dose, in the range of 10-20 mg. This could not be found.

Thus, the applicant proceeded with an alternative approach to apply for a BCS-based biowaiver.

BCS-based biowaiver

The applicant claims that tranylcypromine is BCS class III substance.

According to the ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a BCS class III-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility but not high permeability (BCS class III). Also, *in-vitro* dissolution characteristics of the test and the reference product should be very rapid.The excipients that might affect bioavailability should be qualitatively the same and quantitatively similar and all other excipients should be qualitatively the same and quantitatively similar, unless appropriate justification is provided.

The composition is not qualitatively and quantitatively similar between the test and reference product. The applicant argued that the results from the bioequivalence study (see below) demonstrates that difference in excipients between the 20 mg strength of the test product and Reference Product Jatrosom 20 mg film-coated tablet does not affect aspects of *in vivo* absorption of tranylcypromine. Since the excipients of the two strengths of the test product are qualitative the same and quantitative proportional and excipients of the strengths of the Reference Product are qualitatively the same, the applicant believed that it is reasonable to assume that differences in excipients between 10 mg strengths test and Reference Product will not have any different effect on *in vivo* absorption as in the bioequivalence study conducted at the 20 mg strength.

Study

Methods

This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Tranylcypromine, 20 mg, tablets with Jatrosom, 20 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of R-tranylcypromine and S-tranylcypromine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2022-09-26 and 2022-10-05.

Results

The results from the pharmacokinetic and statistical analysis are presented in Tables below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for R-Tranylcypromine, n=31.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**79.37 ± 35.53**	**39.79 ± 15.28**	**1.00 (0.75 - 1.67)**
Reference	**80.45 ± 28.22**	**39.91 ± 12.51**	**1.00 (0.50 - 4.50)**
***Ratio (90% CI)**	**96.37 (86.44 - 107.45)**	**97.25 (83.33 - 113.50)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for S-Tranylcypromine, n=31.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**541.67 ± 158.02**	**94.05 ± 21.22**	**1.00 (0.75 - 2.67)**
Reference	**554.69 ± 161.86**	**95.18 ± 20.50**	**1.07 (0.50 - 4.50)**
***Ratio (90% CI)**	**97.56 (90.17 - 105.55)**	**98.35 (90.21 - 107.24)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Discussion and overall conclusion
Tranylcypromine is not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with tranylcypromine.

The references submitted by the applicant could not support that the extent of absorption is above 85%.
High solubility has been demonstrated.
Thus, it can be concluded that tranylcypromine is BCS class III substance.

The excipients are not qualitatively the same and quantitatively similar between the test and reference product. However, study showed that the differences in excipients does not affect absorption of tranylcypromine. The results of this study can also be extrapolated to the applied 10 mg strength. Acceptable *in vitro* dissolution data has been submitted. See also section III.1 Quality aspects.

In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: 2care4 Generics ApS
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Tranylcypromine Afortas.

Part II Safety specification
The MAH has submitted the version 0.3 RMP dated 09-Januray-2026 and proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	Hypertensive crisis
Important potential risks	None
Missing information	None

The proposed summary of safety concerns is in line with the RMP version 1.1 for Abbonate film-coated tablet 20 mg (procedure SE/H/2485/001), recently approved and is endorsed.

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

Part V Risk minimisation measures
Routine risk minimisation is suggested.

Additional risk minimisation measures are proposed for patients for the risk 'Hypertensive crisis':
- Educational material: Patient guide, including patient diary.
- Patient alert card.

This is endorsed.

See section VII.3 in this Overview for the key elements.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.3 RMP dated 09-January-2026 is considered acceptable.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Tranylcypromine Afortas, is found adequate.

There are no objections to approval of Tranylcypromine Afortas, from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

Please refer to section VII.3 for information about the condition regarding educational material, patient guide and patient alert card.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  The educational material should contain the following key elements:
  - Patient guide, including patient diary
  - Patient alert card

  Educational material for the patient:
  - signs and symptoms of hypertensive crisis and when to seek advice to seek medical advice
  - the need for tyramine-restricted diet and the relationship between the tyramine-restricted diet and blood pressure increases
  - the dietary advice stating how to follow a low tyramine diet and which products should be avoided.
  - the possible drug interactions
  - the need for regular monitoring of blood pressure

  Patient Alert Card:
  - a statement that the patient is using tranylcypromine,
  - a warning for (tyramine) food- and medication-interactions
  - a predefined section for prescriber contact information. These contact details can be written by the patients themselves on the card in predefined sections.

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to
Abbonate 20 mg film-coated tablet, SE/H/2485/01/MR, regarding content and
Purimmun 50 mg tabletter, SE/H/1655/001/DC, regarding layout.

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-