COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tranylcypromine Glenmark 10 mg and 20 mg film-coated tablets (tranylcypromine sulfate)

NL/H/4812/001-002/DC

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This module reflects the scientific discussion for the approval of Tranylcypromine Glenmark 10 mg and 20 mg film-coated tablets. The marketing authorisation was granted on 5 October 2021. 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
BP	British Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CV	Coefficient of variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ERP	European Reference Product
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Tranylcypromine Glenmark 10 mg and 20 mg film-coated tablets, from Glenmark Arzneimittel GmbH.

Tranylcypromine Glenmark are indicated for the treatment of major depressive episodes in patients with multi-resistant depressive disorder, where adequate treatment with two standard antidepressants (including tricyclic antidepressants) and augmentation with, for example lithium, has not been sufficiently effective.

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 European Reference Products (ERPs) Jatrosom 10 and 20 mg film-coated tablets which have been registered in Germany since 22 September 1999 and 28 November 2007, respectively, by Aristo Pharma GmBH. The ERPs are not registered in the Netherlands.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Tranylcypromine Glenmark 10 mg film-coated tablets are pink to light pink, round, biconvex coated tablets debossed with ‘Y3’ on one side and score line on other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The 20 mg film-coated tablets are pink to light pink, round, biconvex coated tablets debossed with ‘Y73’ on one side and break line on other side. The tablet can be divided into equal doses.

The 10 mg and 20 mg film-coated tablets contain tranylcypromine sulfate corresponding to 10 mg and 20 mg of the active substance tranylcypromine, respectively.

Both strengths of the film-coated tablets are packed in blister packs and container packs. The blister packs are white opaque PVC/PVDC-Alu blister packs in aluminium pouch with molecular sieve as desiccant further packed in cardboard cartons. The container packs are HDPE containers with closure containing molecular sieve as desiccant.

The excipients of both product strengths are:
Tablet core – lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, colloidal silica anhydrous and magnesium stearate.
Film-coating – macrogol, titanium dioxide (E171), talc and Allura red Aluminium lake (E129).

II.2 Drug Substance

The active substance is tranylcypromine sulfate, an established active substance described in the British Pharmacopoeia (BP). The active substance is a white or almost white crystalline powder, soluble in water, very slightly soluble in alcohol and ether, and practically insoluble in chloroform. Tranylcypromine sulfate is a racemic mixture. The molecular structure contains two asymmetric centres. Resolution of the racemic mixture into two enantiomers is possible. One crystalline form is constantly used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of the active substance consists of adequate synthesis steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification is established in-house by the MAH, which is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches of the drug substance. This has been justified since additional information is present in the ASMF on three batches of the active substance.

Stability of drug substance
Stability data on the active substance have been provided for 16 full scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (six months), in accordance with applicable European guidelines. The batches were stored in double polyethylene bags. The drug substance is stable and remains compliant with the specification, no upward or downward trends can be observed. Based on the data submitted, a retest period could be granted of 60 months without special storage requirements.

II.3 Medicinal Products

Pharmaceutical development
The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is

justified and their functions are explained. The MAH used a Quality by Design (QbD) approach to develop generic tablets that are therapeutically equivalent to the reference products. The MAH adequately performed different studies, including a forced degradation study, a solubility study, excipient compatibility studies, formulation optimisation studies and dissolution method development studies. One bioequivalence study was submitted to demonstrate bioequivalence between the 20 mg test and reference medicinal product, which will be discussed in section IV. A biowaiver was requested for the lower strength. To support the bioequivalence, comparative dissolution testing data between the reference product and test product at three pH's have been submitted, in accordance with the Ph. Eur. 5.17.1. The dissolution profile was similar in all the dissolution media covering the entire gastrointestinal pH range studied and almost complete dissolution was achieved within 15 minutes.

Manufacturing process

The manufacturing process is a standard process involving sifting, blending, compaction, milling, lubrication, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented three full scale batches.

Control of excipients

All excipients, except the film-coating, comply with the requirements in the relevant Ph. Eur. monographs. For the film-coating, in-house specifications are applied. The specifications are acceptable.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The products specification includes tests for description, identification, average weight, dissolution, uniformity of dosage units, related substances, assay of tranylcypromine, water content, microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods have been adequately described and validated.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on three full scale batches per strength, demonstrating compliance with the release specification.

Stability of drug products

Stability data on the products have been provided on three batches of each strength stored at 25°C/60% RH (24 months) and at 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-Alu blister pack and HDPE bottle pack. Photostability studies were performed in accordance with ICH recommendations and showed that the products are stable when exposed to light. It can be concluded that no clear trends or significant changes were observed during both the accelerated and long term storage conditions. The proposed shelf life of two years without further storage condition has been accepted.

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 MEB considers that Tranylcypromine Glenmark have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tranylcypromine Glenmark 10 mg and 20 mg film-coated tablets are 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

These products are generic formulations of Jatrosom 10 and 20 mg film-coated tablets, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tranylcypromine sulfate 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 MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study in which the 20 mg test product is compared with the 20 mg reference product. A biowaiver was

requested for the lower 10 mg strength. Both the bioequivalence study and biowaiver will be discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tranylcypromine Glenmark 20 mg film-coated tablets (Glenmark Arzneimittel GmbH, Germany) is compared with the pharmacokinetic profile of the European reference product Jatrosom 20 mg film-coated tablets (Aristo Pharma GmBH, Germany).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been requested for the 10 mg strength, based on the result of the bioequivalence study conducted with the 20 mg strength. The following requirements for waiving studies for an additional strength as listed in the *Guideline on the Investigation of Bioequivalence* are fulfilled:

- Tranylcypromine Glenmark 10 mg and 20 mg tablets are manufactured by the same manufacturer using the same manufacturing process.
- The qualitative composition of both strengths is the same.
- The 10 mg film-coated tablets are dose proportional with the 20 mg film-coated tablets. Thus, the ratio between amount of each excipient to the amount of active substance is the same for both the strengths.
- Appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing

In conclusion, from a pharmacokinetic point of view a biowaiver for the 10 mg strength could be granted.

Bioequivalence study

Design

An open-label, single-dose, randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 23-40 years. Each subject received a single dose (20 mg) of one of the two tranylcypromine formulations. The tablet was orally administered under sodium vapour lamp with 240 ml water after an overnight fasting period of ten hours. There were two dosing periods, separated by a washout period of 13 days. Blood samples were collected prior to drug administration and at 0.16, 0.25, 0.5, 0,67, 0.83, 1.0, 1.25, 1.25, 1.50, 1.75, 2.0, 2,5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24 hours after administration of the products.

The design of the study is acceptable. A bioequivalence study in healthy subjects under fasting conditions is considered 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.

Despite the presence of (+) and (-) enantiomers of tranylcypromine, tranylcypromine was analysed using an achiral assay. In accordance with the *Guideline on the Investigation of Bioequivalence*, individual enantiomers should be measured when all the following conditions are met: (1) the enantiomers exhibit different pharmacokinetics; (2) the enantiomers exhibit pronounced difference in pharmacodynamics; (3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption. The MAH provided data indicating that the absorption rate of the (-) and (+) enantiomers are comparable. Therefore, since condition 3 is not met, the use of an achiral assay is considered justified.

Results

Out of the 32 subjects, 31 subjects were eligible for pharmacokinetic analysis. One subject withdrew from the study on own accord.

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

Treatment N=31	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h
Test	456.13 ± 128.83	463.77 ± 135.09	82.94 ± 17.65	1.50 (0.83-2.50)
Reference	460.75 ± 126.24	468.14 ± 131.09	84.41 ± 17.36	1.25 (0.83-2.50)
***Ratio (90% CI)**	0.992 (0.953-1.034)	0.993 (0.953-1.034)	0.982 (0.939-1.027)	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
CI Confidence interval
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for tranylcypromine are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Tranylcypromine Glenmark 20 mg film-coated tablets is considered bioequivalent with Jatrosom 20 mg film-coated 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 Tranylcypromine Glenmark.

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

Important identified risks	• Hypertensive crisis • Occurrence of convulsion • Orthostatic hypotension • Serotonin syndrome
Important potential risks	• Exposure during pregnancy • Suicidal ideation, suicidal behaviour and acute toxicity • Withdrawal reactions (including delirium)
Missing information	• Exposure through human milk • Exposure to children and adolescents (<18 years old) • Renal toxicity

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information, except for the important identified risk 'hypertensive crisis'.

In line with the other tranylcypromine products registered in the Netherlands, the MAH developed educational material for the important identified risk hypertensive crisis. The material consists of dietary advice for the patient and a patient alert card. The dietary advice is aimed to inform patients about the risk for hypertensive crisis and provide dietary advices for the "tyramine-restricted diet" that patients should adhere to, and explains the relationship between the tyramine-restricted diet and blood pressure increases and the need to monitor the blood pressure during the diet. The patient alert card is aimed to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Jatrosom. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the 20 mg product is similar to the pharmacokinetic profile of the respective reference product. A biowaiver has been granted for the 10 mg product. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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 test consisted of a pilot test with six participants, followed by two rounds with ten 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

Tranylcypromine Glenmark 10 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Jatrosom 10 and 20 mg film-coated tablets. Jatrosom are well-known medicinal products 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.

On the basis of the data submitted, the MEB considered that essential similarity has been demonstrated for Tranylcypromine Glenmark 10 mg and 20 mg film-coated tablets with the reference products, therefore, have granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 October 2021.

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