CBG MEB

Public Assessment Report

Scientific discussion

Tranylcypromine Tiofarma 10 mg, coated tablets

(tranylcypromine sulfate)

NL License RVG: 116661

Date: 4 July 2018

This module reflects the scientific discussion for the approval of Tranylcypromine Tiofarma 10 mg, coated tablets. The procedure was finalised on 16 November 2016. 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
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
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 Tiofarma 10 mg, coated tablets, from TioFarma B.V.

The product is indicated for: the treatment of severe, treatment-resistant depressive disorder irresponsive to two preceding, adequate standard anti-depressive treatments (including tricyclic antidepressants) and augmentation with e.g. lithium.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product previously know as Parnate 10 mg tablets, marketed in the United Kingdom since 15 September 2000. Parnate is now know as Tranylcypromine 10 mg tablets, which has been registered in the United Kingdom by Mercury Pharmaceuticals Ltd, since 6 December 2013. Tranylcypromine sulfate is available for clinical use since more than 50 years in countries worldwide. At the time of this application, Tranylcypromine 10 mg Tablets were not registered in The Netherlands, but could be prescribed with permission from the Health Care Inspectorate (‘artsenverklaring’).

The marketing authorisation has been granted pursuant to Article 10(1).

II. QUALITY ASPECTS

II.1 Introduction

Tranylcypromine Tiofarma tablets are red, round, biconvex, coated, imprinted in black with TRN on one side and plain on the other side. One coated tablet contains 13.70 mg of tranylcypromine sulphate corresponding with 10 mg of tranylcypromine.

The coated tablets are packed in PVC/Alu/Alu blisters and/or HDPE bottles with a polypropylene screw cap.

The excipients are:
Tablet core – microcrystalline cellulose (E460), pregelatinised starch, carmellose sodium (E466); calcium sulfate dehydrate (E516), croscarmellose sodium (E468) and magnesium stearate (E572).
Tablet coating - Opaglos clear (NA 7150), calcium carbonate (E170), hypromellose (E464), polyethylene glycol 6000, talc (E553B), titanium dioxide (E171), ponceau 4R lake (E124), carmoisine lake (E122), aspartame (E951) and sucrose.
Black ink – Shellac (E904), black iron oxide (E172), propylene glycol (E1520) and ammonium hydrochloride.

II.2 Drug Substance

The active substance is tranylcypromine sulfate, an established active substance, described in the British Pharmacopoeia (Ph.Eur.). The active substance is white or almost white, crystalline powder and soluble in water; very slightly soluble in ethanol (96%) and in ether; practically insoluble in chloroform. Tranylcypromine sulphate is a racemic mixture. The molecular structure contains 2 asymmetric centres at carbons 1 and 2 of the cyclopropanic ring. The resolution into 2 enantiomers is possible. The substance show polymorphism, a 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 drug Substance is manufactured in a three step synthesis followed by a conversion into the appropriate salt (sulphate). Acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification or stricter (impurity limits) than the limits included the BP monograph for Tranylcypromine Sulfate. The specification is acceptable in view of the route of synthesis and the various European guidelines. The absence of a limit for the microbiological quality of the drug substance has been justified. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 14 commercial scale batches stored at 25°C/60%RH (up to 60 months) and for 3 batches stored at 40°C/75%RH (6 months). No significant changes were observed during the stability studies. Results of a photostability study performed in accordance with the Note for Guidance on the Photostability Testing of new Active Substances and medicinal Products, have been provided. The drug substance is photo stable. On the basis of the provided stability data the proposed retest period of 60 months without specific storage conditions is acceptable.

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. The test drug product (biobatch) was satisfactorily compared with the UK reference product in dissolution studies and a bioequivalence study has been performed with the UK reference product. Test and reference product showed to be bioequivalent. The discriminative nature of the QC dissolution condition (0.1N HCl as described in the USP monograph of Tranylcypromine Tablets) has been investigated with regard to tablet hardness and medium pH; both appeared to be non-discriminative parameters. The drug product and manufacturing development itself are adequately described and performed.

Manufacturing process
The manufacturing process is a straight forward process using direct compression. The ingredients are mixed and compressed into tablet cores. The cores are coated with four layers of different coatings. The in-process controls appear to have been adequately considered and described.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two commercial scale batches. The product is manufactured using conventional manufacturing techniques. It has been confirmed that process validation for full scale batches will be performed post authorisation.

Control of excipients
The excipients used are well known and are either of Pharmacopoeial quality (Ph Eur) or adequately controlled by other EU regulation (colorants with E-number), and for Opaglos an in-house specification is used. 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, disintegration time, dimensions, water content, uniformity of dosage units (CU), dissolution, assay, related substances, organic impurities, residual solvents and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical except for the number of identity tests performed, the determination of CU (only at release) and the water content. The product specifications broadly cover appropriate parameters for this

dosage form. Satisfactory validation data for the analytical methods have been provided. Batch analytical data two validation batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for two commercial scale batches stored at 25°C/60%RH (18 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in both the proposed HDPE container and the PVC/Alu-Alu blisters. Under both storage conditions the drug product remains within the specification for all parameters tested. With the exception of a fluctuation in the assay, leading to the conclusion that extrapolation is not feasible, no significant changes are observed. Data on the photostability of the drug product (provided in the pharmaceutical development section) showed no change in physical appearance of the drug product and impurities well within acceptable limits.
On the basis of 24 months stability data a shelf-life of 24 months for the drug product, when stored below 25°C, is considered justified.

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 Tiofarma 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 Tranylcypromine Tiofarma 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

This product is a generic formulation of Tranylcypromine 10 mg tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 sulphate 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, MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tranylcypromine Tiofarma 10 mg, coated tablets (Tiofarma B.V., NL) is compared with the pharmacokinetic profile of the reference product Tranylcypromine 10 mg, tablets (Mercury Pharmaceuticals Ltd, UK).

The choice of the reference product in the bioequivalence studies is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

An open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 19-44 years. Each subject received a single dose (10 mg) of one of the 2 tranylcypromine formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. A study under fasting condition is agreed as the reference product can be taken with or without food. The wash-out period of 7 days is long enough to prevent carry-over effects as this is ≥ 5X the reported half-life of tranylcypromine (about 2 hours). The sampling schedule is considered adequate to estimate the PK parameters. The handling and processing of the plasma samples are according to standard procedures.

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

One subjects was withdrawn from the study due to an adverse event and two subjects did not report to the facility for the second period. Therefore, 39 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=39	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	142.8 ± 49.1	33.2 ± 10.1	2.0 (1.0 – 2.75)	2.49 ± 0.5
Reference	139.4 ± 52.5	33.0 ± 10.4	1.5 (1.0 – 3.5)	2.53 ± 0.5
***Ratio (90% CI)**	1.03 (0.98 – 1.08)	1.00 (0.94 – 1.07)	--	--

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 concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tranylcypromine Tiofarma 10 mg, coated tablets is considered bioequivalent with Tranylcypromine 10 mg, tablets.

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 Tiofarma

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypertensive crisis - Occurrence of convulsion - Orthostatic hypotension - Serotonin Syndrome
Important potential risks	- Potential for off-label use, including abuse and dependence - Suicidal ideation, suicidal behaviour and acute toxicity - Withdrawal reactions (including delirium) - Exposure through human milk
Missing information	- Exposure to children and adolescents - Renal toxicity - Exposure during pregnancy

The RMP is acceptable. For the important identified risk 'hypertensive crisis' educational material in the form of a booklet including dietary advice and a patient alert card has been developed. The material should be distributed to psychiatrists and psychiatrists in training, who will provide the patient with the patient material.

A registry study will be performed to monitor the effectiveness of the educational material and the overall occurrence of adverse drug events.

An interim analysis of the registry study will be performed yearly. At the end of the 2-year study period, the dataset will be evaluated to determine whether the educational material provided to patients and prescribers was effective.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tranylcypromine 10 mg, tablets. No new clinical studies were conducted. 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 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 2 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 package leaflet 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 Tiofarma 10 mg, coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Tranylcypromine 10 mg tablets. Tranylcypromine 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.

In two Board meetings of 30 July 2015 and 12 August 2015, the following was discussed: QP declaration, clinical overview and product information concerning risk minimisation. All issues have been resolved.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tranylcypromine Tiofarma with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 16 November 2016.

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