COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tranylcypromine Double-e Pharma 10 mg, film-coated tablets (tranylcypromine sulfate)

NL License RVG: 125926

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This module reflects the scientific discussion for the approval of Tranylcypromine Double-e Pharma 10 mg, film-coated tablets. The marketing authorisation was granted on 12 July 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
CEP	Certificate of Suitability to the monographs of the European 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
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 Double-e Pharma 10 mg, film-coated tablets, from Double-e Pharma Limited.

Tranylcypromine Double-e Pharma is 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 national procedure concerns a generic application claiming essential similarity with the innovator product previously known as Parnate 10 mg tablets, and currently approved in various European countries as a Tranylcypromine film-coated tablets (10 mg) which has clinical experience in the EEA. This European Reference Product (ERP) is not registered in the Netherlands.

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

II. QUALITY ASPECTS

II.1 Introduction

Tranylcypromine Double-e Pharma 10 mg, film-coated tablets are red, round, biconvex tablets imprinted with "10" on one side. The film-coated tablets contain tranylcypromine sulfate corresponding with 10 mg of tranylcypromine base.

The film-coated tablets are packed in white HDPE bottles with child-resistant screw caps with integrated desiccant.

The excipients are:
Tablet core – microcrystalline cellulose (E460), pregelatinised starch, colloidal silica anhydrous and magnesium stearate (E572).
Tablet coating – Opadry II red 85F250100 comprising polyvinyl alcohol (E1203), polyethylene glycol 3350, talc (E553b), FD&C Red No. 40 Aluminium Lake (E129), titanium dioxide (E171) and carmine (E120).

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 three 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 in line with the specification of the ASMF holder, with additional requirements for particle size distribution. The tests for potentiometric assay and elemental impurities have not been adopted from the ASMF holder. This is justified. The specification of the drug substance is acceptable and is considered adequate to control the quality. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of the drug 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 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 are explained. The compatibility of the drug substance with proposed excipients was demonstrated.

One bioequivalence study was submitted to demonstrate bioequivalence between the test and reference medicinal product, which will be discussed in section IV. To support the bioequivalence study, comparative dissolution testing data between the reference product and test product at three pH's have been submitted. Only the study in pH 1.2 showed comparable dissolution profiles. No similarity was demonstrated at pH 4.5 and 6.8, due to a lag-time before disintegration for the sugar coated reference product. It has been adequately justified that this observed difference does not impact mouth taste, oesophagus passage or degradation in the gastrointestinal tract. The discriminatory nature of the Quality Control dissolution method has been adequately justified.

Manufacturing process

The manufacturing process has been adequately validated according to relevant European guidelines. The manufacturing process consists of five phases: pre-blending, blending, tabletting, film-coating and packaging. The manufacturing process was described in sufficient detail. Process validation data on the product have been presented for two pilot scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

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

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specification includes tests for appearance, identification of tranylcypromine and titanium dioxide, resistance to crushing, disintegration, average mass, uniformity of dosage units, dissolution, assay of tranylcypromine, related substances, water content and microbiological purity. Resistance to crushing is only performed during stability testing. Identification tests, average mass and uniformity of dosage units are only performed during release testing. The risk evaluation on elemental impurities and nitrosamines have been adequately performed. The results justify no further controls for these possible contaminants. The release and shelf life limits are identical for all test parameters. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

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

Stability of drug product

Stability data on the product has been provided for two pilot scale batches stored at 40°C/75% RH (six months) and 25°C/60% RH (24 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in HDPE bottles with white round plastic child-resistant tamper-evident screw cap with integrated silica gel desiccant. Photostability studies were performed in accordance with ICH recommendations and showed that the product is 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 36 months 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 Double-e Pharma 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 Double-e Pharma 10 mg, film-coated tablets 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 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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tranylcypromine Double-e Pharma 10 mg, film-coated tablets (Rivopharm SA, Switzerland) is compared with the pharmacokinetic profile of the European reference product Tranylcypromine 10 mg tablets (Dales Pharmaceuticals Ltd., UK).

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.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy subjects, aged 22-40 years. Each subject received a single dose (10 mg) of one of the two tranylcypromine formulations. The tablet was orally administered with 240 ml water after an overnight fasting period of ten hours. There were two dosing periods, separated by a washout period of seven days. Blood samples were collected prior to drug administration and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, and 12.00 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The plasma samples of subjects were analysed for R-tranylcypromine and S-tranylcypromine concentration. 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

All 16 subjects were eligible for pharmacokinetic analysis. Table 1, 2 and 3 show the pharmacokinetic parameters of R-, S- and total tranylcypromine, respectively.

Table 1. Pharmacokinetic parameters (AUC_{0-t} and C_{max} (geometric LS means), $AUC_{0-\infty}$ (arithmetic mean), t_{max} (median, range)) of R-tranylcypromine under fasted conditions.

Treatment N=16	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	5525.5	6133.9	3617.4	1.00 (0.50 - 1.67)	1.88
Reference	5192.9	5543.2	3814.0	1.00 (0.50 - 1.33)	1.83
***Ratio (90% CI)**	1.064 (0.973 – 1.163)	--	0.959 (0.812 – 1.108)	--	--
CV (%)	14.4	--	25.4	--	--

$AUC_{0-\infty}$ 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
CV Coefficient of variation
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (AUC_{0-t} and C_{max} (geometric LS means), $AUC_{0-\infty}$ (arithmetic mean), t_{max} (median, range)) of S-tranylcypromine under fasted conditions.

Treatment N=16	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	72133	81219	23796	1.17 (0.75 – 2.00)	1.91
Reference	67859	72507	24043	1.33 (0.75 - 1.67)	1.82
***Ratio (90% CI)**	1.063 (0.987 – 1.145)	--	0.990 (0.907 – 1.08)	--	--
CV (%)	12.0	--	14.1	--	--

$AUC_{0-\infty}$ 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
CV Coefficient of variation
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 3. Pharmacokinetic parameters (AUC_{0-t} and C_{max} (geometric LS means), $AUC_{0-\infty}$ (arithmetic mean), t_{max} (median, range)) of total tranylcypromine under fasted conditions.

Treatment N=16	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	77786	87314	26988	1.00 (0.75 - 1.67)	1.91

Reference	73208	78001	26995	1.17 (0.75 - 1.67)	1.80
***Ratio (90% CI)**	1.063 (0.987 – 1.144)	--	0.9997 (0.912 - 1.096)	--	--
CV (%)	11.9	--	14.8	--	--

$AUC_{0-\infty}$ 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
CV Coefficient of variation
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} for R-, S- and total tranylcypromine are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Tranylcypromine Double-e Pharma 10 mg, film-coated tablets is considered bioequivalent with Tranylcypromine 10 mg 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 Double-e Pharma.

Table 4. 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 first part of educational material is dietary advice for the patient, with the following information included:

- signs and symptoms of hypertensive crisis and when to seek advice to seek medical attention;
- 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.

Another part of the booklet is patient alert card with the following information:

- a statement that the patient is using tranylcypromine;
- a warning for tyramine containing food- and medication-interactions;
- a predefined section for prescriber contact information.

For the evaluation of effectiveness of the additional risk minimisation measures the MAH shall actively follow up reported spontaneous cases for hypertensive crisis. For this purpose, developed internal questionnaire to be filled each time respective case received by the company.

For all other safety concerns, routine risk minimisation measures including product labelling and prescription only medicinal status are considered adequate to communicate risks associated with use of Tranylcypromine Double-e Pharma.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tranylcypromine. 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 (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 Dutch.

The test consisted of 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 Double-e Pharma 10 mg, film-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.

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 Double-e Pharma 10 mg, film-coated tablets with the reference product, therefore, have granted a marketing authorisation. The national procedure was finalised with a positive outcome on 12 July 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