CBG MEB

Public Assessment Report

Scientific discussion

Tetrabenazine SUN 12.5 mg and 25 mg tablets

(tetrabenazine)

NL/H/3504/001-002/DC

Date: 30 April 2019

This module reflects the scientific discussion for the approval of Tetrabenazine SUN 12.5 mg and 25 mg tablets. The procedure was finalised on 5 August 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
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
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
USP-NF	United States Pharmacopoeia National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tetrabenazine SUN 12.5 mg and 25 mg tablets from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for hyperkinetic motor disorders with Huntington's chorea.

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 innovator product Xenazine 25 mg tablets which has been registered in the UK by Lundbeck UK LLP since 23 October 1995. The innovator product is only available as 25 mg strength. For the Netherlands reference is made to Xenazine on the principle of a European Reference Product.

The concerned member states (CMS) involved in this procedure were Germany, Spain, Italy and the United Kingdom.

The marketing authorisation for the 25 mg strength has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic medicinal product). For the 12.5 mg strength the legal base is Article 10(3) of Directive 2001/83/EC (hybrid medicinal product).

II. QUALITY ASPECTS

II.1 Introduction

Tetrabenazine SUN is a tablet in two strengths:

The 12.5 mg strength is a white to off-white, circular, flat faced bevelled edge uncoated tablet with "1" on one side and plain on the other site. Each tablet contains 12.5 mg tetrabenazine.

The 25 mg strength is a yellow, circular, flat faced bevelled edge uncoated tablet debossed with "179" on one side and scored on the other side. Each tablet contains 25 mg tetrabenazine and can be divided into equal halves.

Tetrabenazine SUN is packed in a white round high-density polyethylene (HDPE) tablet container with a child resistant, tamper-evident polypropylene (PP) screw cap with mounted desiccant.

The excipients are lactose anhydrous, maize starch, sodium starch glycolate, talc, colloidal anhydrous silica and magnesium stearate. The 25 mg strength also contains iron oxide yellow (E172).

The two tablet strengths are dose proportional (with the colourant replaced in the 12.5 mg strength by lactose as filler).

II.2 Drug Substance

The active substance is tetrabenazine, an established active substance that is not described in a pharmacopoeia. Tetrabenazine is a white to almost white, crystalline powder. It does not exhibit polymorphism. Tetrabenazine is soluble at low pH and remains constant at increased pH until pH 6.2 – 9.0 (poorly soluble). It is soluble in chloroform, sparingly soluble in methanol and insoluble in water. Tetrabenazine has two chiral centres. The substance is a racemic mixture.

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 consists of four steps. Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process control and intermediate specifications are applied.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of ASMF, with additional tests on particle size distribution. The limits for particle size distribution should be evaluated according to the values for this parameter of the drug substance in the biobatch. For completion of the evaluation, these values should be submitted.
Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The stability has been studied with at least three production batches stored during at least 36 months at 25°C/60% RH and six months at 40°C/75% RH. Based on the stability results, a retest period and storage condition of five years, no special storage conditions is justified.

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 objective of the development was to produce a product containing tetrabenazine as generic product of the originator (25 mg strength) with equivalent quality, efficacy and safety. Studies were performed such as characterisation of a batch of the originator, *in vitro* dissolution of originator tablets and investigations of formulations and process parameters. The development studies include Quality by Design (QbD) elements, however, the dossier is a traditional dossier and no design spaces are included. Functionality of the score line of the 25 mg tablet has been demonstrated according to the European Pharmacopoeia (Ph.Eur.) test criteria.

A bioequivalence study has been performed with the 25 mg strength and a biowaiver is proposed for the 12.5 mg strength. Similar dissolution profiles at pH 1.2, 4.5 and 6.8 between the product strengths have been provided (f_2>50).

Manufacturing process
The manufacturing process is a standard process. The main steps in the manufacturing process are: dispensing of the raw materials and preparation of dry granulate, preparation of pre-compression blend and tablet compression. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two production scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur or the United States Pharmacopoeia National Formulary (USP-NF). The colourant (E172) complies with the EU Directive. The quality standards of some of the excipients include also tests and limits for functionality related characteristics relevant for quality of the formulation and manufacturing process. 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, tablet dimensions. identity, assay, related substances, uniformity of dosage units, water content, dissolution, microbiological purity, resistance to crushing and uniformity of mass of the subdivided 25 mg tablet. Hardness and average mass are also tested during the production process. The release and shelf-life requirements/limits are identical with the exception of the limit for water content, related substances; the shelf-life limits for these

parameters are slightly wider. 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 two production scale batches per product strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two production scale batches per product strength. The batches have been stored up to 12 months (two batches) and 36 months (two batches) at 25°C/60% RH, and all batches have been stored during 6 months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. All parameters were well within the proposed specification limits. The proposed shelf-life of two years, without special storage conditions, in the proposed tablet container is justified.
A photostability study has been performed, according to ICH Q1B guideline; the tablets are light resistant. An in-use study (28 days) has been performed with the 25 mg tablet packaged in the tablet container. In-use stability will also be studied in due time, of both product strengths, with batches first stored during the shelf-life; this has been committed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of animal origin present in the product, except lactose. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tetrabenazine SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- To continue the on-going long term studies up to 36 months.
- The in-use studies with both tablet strengths will be performed for product first stored during the approved shelf-life.
- To finalise the child resistance tests of the container closure per EN–ISO 8317:2015 before the product is marketed, in support of the claim for child resistance of the closure. The results will be available at the request of the EU Authorities.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tetrabenazine SUN 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 Xenazine 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tetrabenazine 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 member states agreed 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tetrabenazine SUN 25 mg tablets (Sun Pharmaceutical Industries Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Xenazine 25 mg tablets (Lundbeck UK LLP, UK).

The choice of the reference product
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
Biowaiving for the 12.5 mg tablets based on the bioequivalence study with the highest strength of 25 mg can be granted as:

- The strengths have been manufactured by the same process and manufacturer.
- The pharmacokinetics of tetrabenazine can be considered dose linear.
- The compositions are qualitatively similar and dose proportional (the deviation of 0.2 mg from dose proportionality for lactose is considered negligibly small).
- Dissolution tests resulted in similar dissolution profiles as compared to the 25 mg strength at three different media (0.1N HCl, pH 4.5 and pH 6.8).

Design
A single-dose, open-label, randomised, two-treatment, replicate, two-sequence, four-period cross-over bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 23-44 years. Each subject received a single dose (25 mg) of one of the two tetrabenazine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of seven or eight days. The design followed was: TRTR or RTRT (T=test product; R=reference product).

Blood samples were collected before dosing and at 0.17, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.83, 1.0, 1.25, 1.5, 2, 4, 6, 8, 10, 14, 18, 24 and 30 hours after administration of the products.

The design is acceptable. A replicate design was applied to use the observed intra-subject variability of the reference for C_{max} for scaling the acceptance range. As tetrabenazine can be taken regardless of food, a study under fasting conditions is acceptable. The half-life of tetrabenazine is about three hours. Therefore plasma sampling until 30 hours after dosing and wash-out period of 7-8 days would be sufficient.

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 subject did not report to the clinic for period II and was lost to follow-up. Another subject dropped out just after dosing in period IV due to vomiting. Therefore 54 subjects were eligible for pharmacokinetic analysis.

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

Treatment N= 54	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	869 ± 675	1027 ± 784	319 ± 296	0.60 0.17 – 14	10.5 ± 15.1
Reference	925 ± 1128	1074 ± 1293	334 ± 311	0.55 0.25 – 14	8.7 ± 6.5
***Ratio (90% CI)**	0.99 0.93 - 1.06	1.02 0.94 - 1.10	0.92 0.83 - 1.01	--	--

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

**ln-transformed values*

Conclusion on bioequivalence study
Widening of the acceptance intervals was allowed but, based on the study results, proved not to be necessary. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tetrabenazine SUN is considered bioequivalent with Xenazine.

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 Tetrabenazine SUN.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Depression • Suicidal Ideation • Parkinsonism • Neuroleptic Malignant Syndrome • Sedation/Somnolence • Akathisia • Dysphagia • Anger • Aggression • Hypersensitivity- associated reactions leading to skin rash of varying types, pruritus and urticaria
Important potential risks	• Exposure to drug during pregnancy • Exposure to drug during breastfeeding • Drug-Drug Interactions (CYP2D6 inhibitors e.g. fluoxetine, paroxetine, quinidine, duloxetine, terbinafine, amiodarone and sertraline)

	• Carcinogenicity/Genotoxicity • Hepatic Impairment • QTc Prolongation • Overdose
Missing information	• Paediatric exposure • Off-label use

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xenazine. 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 test consisted of: a pilot test, 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tetrabenazine SUN 12.5 mg and 25 mg tablets have a proven chemical-pharmaceutical quality. The 25 mg strength is a generic form of Xenazine 25 mg; the 12.5 mg strength is a hybrid form. Xenazine 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tetrabenazine SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 August 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Deletion of a non-significant specification parameter	NL/H/3504/ 001/G	IB	19-6-2017	19-7-2017	Approval	-
Replacement or addition of a supplier	NL/H/3504/ 001-002/IA/003	IA	1-2-2018	1-3-2018	Approval	-
Other variation	NL/H/3504/ 001-002/IA/002	II	15-5-2018	5-6-2018	Approval	-