IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

TUXERDIV 1.5 mg film-coated tablets
Cytisinicline
PA23514/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Tuxerdiv (cytisinicline) 1.5 mg film-coated tablets to Vale Pharmaceuticals Limited on 21st of April 2023 for the following indication:

Smoking cessation and reduction of nicotine cravings in adult smokers who are willing to stop smoking. The treatment goal of TUXERDIV is the permanent cessation of the nicotine-containing products use.

This is a generic application in accordance with article 10.1 of the Directive 2001/83/EC, as amended. Tuxerdiv 1.5mg film-coated tablet is considered essentially similar to the reference medicinal product Tabex 1.5 mg film-coated tablets, Sopharma, Poland, which has been authorized within the Community for more than ten years.

Tuxerdiv 1.5 mg film-coated tablets are subject to prescription.

One package of Tuxerdiv (100 tablets) is sufficient for a complete treatment course. The duration of therapy is 25 days according to a specific dosing schedule please review the Product Information for full prescribing information.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Tuxerdiv 1.5 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Cytisinicline
Pharmacotherapeutic classification (ATC code)	N07BA - Drugs used in nicotine dependence
Pharmaceutical form and strength(s)	Film-coated tablet, 1.5 MILLIGRAMS
Marketing Authorisation Number(s) in Ireland (PA)	PA23514/001/001
Marketing Authorisation Holder	Adamed Pharma S.A.
MRP/DCP No.	N/A

II. QUALITY ASPECTS

II.1. Introduction

This application is for Tuxerdiv 1.5 mg film coated tablets.

II.2 Drug substance

The active substance is cytisine (cytisinicline), an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The medicinal product contains 1.5 mg of cytisine (cytisinicline).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopeial monograph for coated tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation have been provided, assuring consistent quality of Tuxerdiv 1.5 mg film coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Tabex film-coated tablets, 1.5 mg on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

The applicant has not conducted environmental risk assessment (ERA) studies; a justification for their absence is provided. Since Tuxerdiv 1.5 mg film-coated tablets are intended for generic substitution, no increased exposure to the environment is expected. Additional studies on environmental risk are therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of cytisinicline are well known. As cytisinicline is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview

based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cytisinicline is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is overall in accordance with that accepted for the reference product Tabex 1.5 mg film-coated tablets marketed by Sopharma Warszawa Sp. z.o.o.

For this generic application, the applicant has submitted one a bioequivalence study in which the pharmacokinetic profile of the test product Tuxerdiv 1.5 mg film coated tablets is compared with the pharmacokinetic profile of the reference product Tabex® 1.5 mg film-coated tablets in accordance with provisions laid down in the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**.

A randomised, crossover bioequivalence study was carried out, Tuxerdiv (cytisinicline) 1.5 mg film coated tablets was compared to the reference product Tabex® 1.5 mg film-coated tablets. Based on the pharmacokinetic parameters of active substance the reference tablet Tabex® 1.5 mg film-coated tablets marketed by Sopharma Warszawa Sp. z.o.o., and Tuxerdiv (cytisinicline) 1.5 mg film coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Pharmacokinetic properties of cytisinicline are well known. After oral administration, cytisinicline was quickly absorbed from the gastrointestinal tract. The mean maximum plasma concentration of 15.55 ng/ml was achieved after a mean of 0.92 hours. Cytisinicline was slightly metabolised, 64% of the dose was excreted unchanged in the urine within 24 hours. The mean half-life in plasma was approx. 4 hours. There is no data in renally and hepatically impaired patients and the influence of food on the exposure of Cytisinicline is unknown.

IV.3 Pharmacodynamics

Pharmacodynamic properties of cytisinicline are well known. The use of Tuxerdiv 1.5mg film coated tablets allows for a gradual reduction of nicotine dependence by relieving withdrawal symptoms. The active ingredient of Tuxerdiv 1.5mg film coated tablets is a plant alkaloid cytisinicline (found, among others, in seeds of golden chain, genus Laburnum), with a chemical structure similar to nicotine. The action of cytisinicline is similar to that of nicotine, but in general weaker. Cytisinicline competes with nicotine for the same receptors and gradually displaces nicotine due to its stronger binding.

IV.4 Clinical Efficacy

As cytisinicline is a widely used, well-known active substance, the applicant has not provided additional clinical studies and further studies are not required in accordance with article 10.1 of the Directive 2001/83/EC, as amended. The submitted clinical overview based on literature review is, thus, appropriate and adequate.

IV.5 Clinical Safety

The submitted clinical overview on the safety of cytisinicline based on literature review is appropriate and adequate. Please review the product information for Tuxerdiv 1.5mg film coated tablets for details on the contraindications to the use, warnings, interactions and potential adverse reactions.

Risk Management Plan (RMP)
The applicant 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 Tuxerdiv 1.5mg film-coated tablets.
Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

Summary of safety concerns

Important identified risks	• None
Important potential risks	• None
Missing information	• None

Periodic Safety Update Report (PSUR)

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.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

To fulfil requirements for Tuxerdiv (cytisinicline) 1.5 mg film coated tablets to be judged as a generic medicinal product approved under article 10.1 of the Directive 2001/83/EC, as amended, and in order to provide adequate bridging data on efficacy and safety of the test product (Tuxerdiv 1.5 mg film coated tablets) to the reference product (Tabex® 1.5 mg film-coated tablets.) the report of a bioequivalence study comparing the pharmacokinetic properties of the test product and reference product in accordance with provisions laid down in the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, has been submitted. The criteria used to assess bioequivalence between the test and reference products were fulfilled. Therefore, Tuxerdiv 1.5mg film-coated tablets can be considered bioequivalent to the reference product (Tabex® 1.5 mg film-coated tablets from Sopharma Warszawa Sp. z.o.o.).

V. OVERALL CONCLUSIONS

Therefore, Tuxerdiv 1.5mg film-coated tablets can be considered bioequivalent to the reference product (Tabex® 1.5 mg film-coated tablets from Sopharma Warszawa Sp. z.o.o.).

Tuxerdiv 1.5mg film-coated tablets is a generic form of Tabex® 1.5 mg film-coated tablets. Tabex is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is overall consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Tuxerdiv 1.5 mg film coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The HPRA, on the basis of the data submitted considered that Tuxerdiv 1.5 mg film coated tablets was the same as the reference product and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable

VI. REVISION DATE

5 years from the finalisation of the procedure.

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC sections 1-9	21st April 2023	20th April 2028
Transfer	N/A	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Adamed Pharma S.A. New PA number: PA23514/001/001	N/A	16th June 2023