IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Varenicline Ascend 0.5 mg Film coated tablet
Varenicline tartrate
PA23429/004/001

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 Varenicline Ascend 0.5 mg Film-coated Tablets & Varenicline Ascend 1 mg Film-coated Tablets, from Ascend GmbH, on 31st January 2025 for the use as an aid to smoking cessation in adults.

This application for a marketing authorisation was submitted via a decentralised procedure in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as an 'generic' application.

Ireland was the Reference Member State (RMS) and the only Concerned Member States (CMS) was Germany.

These are prescription-only medicinal products.

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	**For 0.5 mg:** Varenicline Ascend 0.5 mg Film coated Tablets **For 1 mg:** Varenicline Ascend 1 mg Film coated Tablets **For 0.5 mg & 1 mg:** Varenicline Ascend 0.5 mg Film coated Tablets Varenicline Ascend 1 mg Film coated Tablets
Name(s) of the active substance(s) (INN)	Varenicline tartrate
Pharmacotherapeutic classification (ATC code)	N07BA03
Pharmaceutical form and strength(s)	0.5mg & 1mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA23429/004/001-003
Marketing Authorisation Holder	Ascend GmbH
MRP/DCP No.	IE/H/1246/001-003/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for
For 0.5 mg: Varenicline Ascend 0.5 mg film coated Tablets
For 1 mg: Varenicline Ascend 1 mg film coated Tablets
For 0.5 mg & 1 mg: Varenicline Ascend 0.5 mg film coated Tablets
Varenicline Ascend 1 mg film coated Tablets

II.2 Drug substance

The active substance is Varenicline Tartrate 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

Each 0.5 mg film-coated tablet contains 0.5 mg of varenicline (as tartrate).
Each 1 mg film-coated tablet contains 1 mg of varenicline (as tartrate).

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 or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, 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 has been provided, assuring consistent quality of Varenicline Ascend 0.5 mg & 1 mg Film-coated Tablets

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Champix on the European market. No new preclinical data have been submitted.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Varenicline Ascend 0.5 mg and 1 mg is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of varenicline are well known. As varenicline is a widely used, well-known active substance, the applicant has not provided additional studies. This is acceptable for this type of application. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Varenicline tartrate is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Champix marketed by MAH.

This is a generic application. No clinical trials (bioequivalence studies) have been carried out on the product as a BCS based bio-waiver has been requested and accepted for varenicline tartrate as per Appendix III of guideline on the investigation of bioequivalence (Doc.Ref.:CPMP/EWP/QWP/1401/98 Rev.1/Corr **).

The submitted clinical efficacy and safety overviews are based on the reference product data and on recent clinical data available in literature which further corroborate the positive risk-benefit balance of varenicline intended for oral use.

IV.2 Pharmacokinetics

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady state. Plasma protein binding of varenicline is low (< 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes in vitro, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Elimination

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Linearity/Non-linearity

Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated 1 to 3 mg/day doses.
Absorbtion and bioavailabilty, distribution, metabolism, elimination, dose proportionality and time dependence, target/special populations, interactions, relationship between concentration and effect.

IV.3 Pharmacodynamics

Mechanism of action

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of Varenicline in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

IV.4 Clinical Efficacy

No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

No additional safety clinical studies to demonstrate safety have been included in the application.

Risk Management Plan (RMP)
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 Varenicline Ascend 0.5mg & 1mg Film-coated Tablets.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	Use in patients with CVD Use in pregnancy

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This is a generic application, the application dossier has been submitted in accordance with the Directive 2001/83/EC, as amended as a generic 10(1) application.

The reference product is well established in the EU being authorised since 2006. Varenicline tartrate has demonstrated efficacy and has a well-established documented safety profile.

This is a generic application. No clinical trials (bioequivalence studies) have been carried out on the product as a BCS based bio-waiver has been requested and accepted for varenicline tartrate as per Appendix III of guideline on the investigation of bioequivalence (Doc.Ref.:CPMP/EWP/QWP/1401/98 Rev.1/Corr **).

The product information is in line with that of the reference product.

V. OVERALL CONCLUSIONS

Varenicline Ascend 0.5 mg & 1 mg Film-coated Tablets is a generic form of Champix. Champix is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

An acceptable biowaiver has been requested in compliance with the CHMP guidance documents. The SmPC is 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 Varenicline Ascend 0.5 mg & 1 mg Film-coated Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

05.12.2029