LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Varenicline Newbury
(varenicline tartrate)

SE/H/2196/01-03/DC

This module reflects the scientific discussion for the approval of Varenicline Newbury. The procedure was finalised on 2024-06-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Varenicline Newbury, 0,5 mg, 1 mg, 0,5 mg + 1 mg, film-coated tablet.

The active substance is varenicline tartrate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Varenicline Newbury, 0,5 mg, 1 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Newbury Pharmaceuticals AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IS as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is CHAMPIX 1 mg Film-coated tablet authorised in EU since 2006, with Pfizer Europe MA EEIG as marketing authorisation holder.

The reference product used in the bioequivalence study is CHAMPIX 1 mg Film-coated tablet from BE with Pfizer Europe MA EEIG as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of varenicline are well known. As varenicline is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Varenicline Newbury is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Varenicline Newbury from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Varenicline with the reference product Champix.

Pharmacokinetic properties of the active substance
Absorption: Absorption is virtually complete after oral administration and systemic availability is high. Following an oral dose of varenicline maximal plasma concentrations occur at approximately 3-4 hours.

The pharmacokinetics of varenicline is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated 1 to 3 mg/day doses.

Elimination: The terminal half-life is 24 hours.

Study C21101
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Varenicline, 1 mg, tablets with Champix, 1 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of varenicline were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 2021-04-05 and 2021-04-26.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for varenicline, n=24.

Treatment	AUC_{0-72h} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**95.373 ± 23.3834**	**5.421 ± 0.9620**	**2.50 (1.00-5.00)**
Reference	**96.395 ± 23.2645**	**5.565 ± 1.2188**	**2.50 (1.00-5.00)**
***Ratio (90% CI)**	**98.18 (90.92-106.02)**	**97.96 (90.74-105.74)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

A biowaiver was sought for the additional strength of 0.5 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 0.5 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of varenicline is linear between 0.1 mg and 3 mg.

Based on the submitted bioequivalence study, Varenicline is considered bioequivalent with Champix.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Varenicline Newbury.

Safety specification

The MAH has submitted the version 0.1 RMP dated 2021-08-23 and proposed the following summary safety concerns, which are in line with the reference product:

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• None
Missing information	• Use in Patients with Cardiovascular Disease (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.

Summary of the RMP
The submitted Risk Management Plan, version 0.1 signed 2021-08-23 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 language used for the purpose of user testing the PL was English.

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

The quality of the generic product, Varenicline Newbury, is found adequate. There are no objections to approval of Varenicline Newbury from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC
N/A

VII. APPROVAL

The decentralised procedure for Varenicline Newbury, 0,5 mg, 1 mg, 0,5 mg + 1 mg, film-coated tablet was positively finalised on 2024-06-05.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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