LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Civarenix
(varenicline tartrate)

SE/H/2482/01-03/DC

This module reflects the scientific discussion for the approval of Civarenix. The procedure was finalised on 2024-12-18. 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 Civarenix, 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 Civarenix, 0,5 mg, 1 mg, 0,5 mg + 1 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, CZ, DK, and IT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Champix, 0,5 mg, Film-coated tablet authorised in the union since 2006, with Pfizer Europe MA EEIG as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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

Pharmacology/Pharmacokinetics/Toxicology
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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Civarenix 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 Civarenix from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS)-based biowaiver and no bioequivalence study has been submitted. The applicant claims that varenicline is a BCS class I substance.

According to the ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a BCS-based biowaiver is applicable for an immediate release oral dosage form with systemic action, and the drug product is the same dosage form and strength as the reference product. Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver. BCS-based biowaivers are applicable for drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS class I) or low permeability (BCS class III). Also, *in vitro* dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be qualitatively the same and quantitatively similar.

Discussion and overall conclusion
Varenicline is not considered to have a narrow therapeutic index.

Based on the submitted data it can be concluded that the extent of absorption is above 85% and the quality criteria for solubility have been fulfilled. It can be concluded that the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I).

All the excipients are considered qualitatively the same except for the addition of ascorbic acid as scavenger with the purpose of avoiding nitrosamine formation and the film coating components. The differences in excipients are acceptable. None of the excipients are likely to affect absorption.

The quality criteria for *in vitro* dissolution have been fulfilled.

In conclusion, the justification for a BCS-based biowaiver can be accepted.

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 Civarenix.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2023-07-20 and proposed the following summary safety concerns:

Summary of safety concerns	
Important Identified Risk	• None
Important Potential Risk	• None
Missing information	• Use in Patients with Cardiovascular Disease (CVD) • Use in Pregnancy

Assessor's comment: Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate. It is in line with the summary of safety concerns of the originator Champix.

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 2023-07-20 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Champix, EMEA/H/C/000699,

regarding the content and Succinato de Solifenacina Combino, PT/H/0547/001-002/DC, regarding the layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Civarenix, is found adequate. There are no objections to approval of Civarenix, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable.The product information is acceptable. The benefit/risk is considered positive, and 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 Civarenix, 0,5 mg, 1 mg, 0,5 mg + 1 mg, Film-coated tablet was positively finalised on 2024-12-18.

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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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