COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Varenicline CF 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets (varenicline tartrate)

NL/H/5189/001-003/DC

Date: 10 December 2025

This module reflects the scientific discussion for the approval of Varenicline CF 0.5 mg, 1 mg and 0.5 mg + 1mg, film-coated tablet. The procedure was finalised on 20 January 2025. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
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
EEA	European Economic Area
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Varenicline CF 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets, from Centrafarm B.V.

The product is indicated for smoking cessation in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Champix 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/06/360) since 25 September 2006.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Finland, France, Luxembourg, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Varenicline CF 0.5 mg and 1 mg are film-coated tablets. The tablets are presented in two strengths which can be distinguished by their colour, size and debossing.

Varenicline CF 0.5 mg
White to white-off, capsular shaped, biconvex film-coated tablets debossed with “C2” on one side and plain on other side. The film-coated tablets are 8.15 mm ± 0.2 mm long and 4.15 mm ± 0.2 mm wide. Each tablet contains 0.5 varenicline, as varenicline tartrate, as active substance.

Varenicline CF 1 mg
Light blue, capsular shaped, biconvex film-coated tablets debossed with “C1” on one side and plain on other side. The film-coated tablets are 10.15 mm ± 0.2 mm long and 5.15 mm ± 0.2 mm wide. Each tablet contains 1 mg varenicline, as varenicline tartrate, as active substance.

The excipients are:
Tablet core – cellulose microcrystalline (E468), maltodextrin (E1400), croscarmellose sodium (E468) and stearic acid (E570).
Film-coating – hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b) and blue indigo carmine (E132; only in the 1 mg tablets).

The two tablet strengths are dose proportional.

The film-coated tablets are either packed in polyvinylidene chloride/polyvinyl chloride /polyethylene/polyvinylidene chloride aluminium (PVdC/PVC/PE/PVdC aluminium) blister packs or in a high-density polyethylene (HDPE) bottle with white opaque polypropylene fine ribbed 38 mm screw cap.

II.2 Drug Substance

The active substance is varenicline tartrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Varenicline tartrate in salt form is a pale brown powder and is soluble in water and insoluble in methanol. Varenicline tartrate exhibits stereoisomer and polymorphism; for this product polymorphic form B is consistently manufactured.

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 five stages with four intermediates and one starting material. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets in-house requirements. There is no compendial monograph available for this substance. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance. Based on the data submitted, a retest period could be granted of 36 months if stored in a well-closed container at 15°C to 35°C under nitrogen atmosphere.

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 explained. The choices of the packaging and manufacturing process are justified in relation to the innovator.

Manufacturing process

The tablets are manufactured by dry granulation followed by compression. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. monographs for each of the tablet core excipients and the functionality-related characteristics are included. The excipients in the film-coating all comply with EU 1130/2011 on food additives as well as the Ph.Eur. or EU 231/2012. 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 description, average mass, uniformity of mass, uniformity of dosage units, identification of drug substance, titanium dioxide and colourant, disintegration time, water content, dissolution, related substances, assay, microbiological examination and impurities. The release and shelf-life acceptance limits are only not identical for water content. The limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. The report states that the risk of a specific impurity is within acceptable daily intake according to EMA's Q&A Appendix 1 (Appendix 1 to Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products).

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three full scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. An in-use stability study was performed and based on the results, no in-use shelf-life needs to be claimed. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Varenicline CF is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Champix which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Varenicline tartrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Varenicline CF 1 mg, film-coated tablets (Centrafarm B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Champix 1 mg, film-coated tablets (Pfizer Europe MA EEIG, Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements according to the EMA Bioequivalence guideline are met for a waiver for the 0.5 mg strength:

- both strengths (0.5 mg and 1 mg) are manufactured by the same manufacturing process,
- the qualitative composition of both strengths is the same,
- the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
- appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values at pH 1.2, 4.5 and 6.8 were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence study

Design

An open-label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19-44 years. Each subject received a single dose (1 mg) of one of the two varenicline tartrate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 18, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Varenicline tartrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of varenicline tartrate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting

conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
Two subjects were withdrawn from the study due to adverse events (vomiting). All other 30 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=30	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	106 ± 15	5.3 ± 0.6	2.67 (0.67 – 4.50)
Reference	106 ± 17	5.3 ± 0.7	2.00 (1.00 – 4.50)
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	1.01 (0.97 – 1.05)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
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 Varenicline CF 1 mg is considered bioequivalent with Champix 1 mg.

The results of the study with 1 mg formulation can be extrapolated to the other strength of 0.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Varenicline CF. At the time of approval, the most recent version of the RMP was version 1.0, signed 10 June 2020.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	• Use in patients with cardiovascular disease • Use in pregnancy

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 Champix. 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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Varenicline CF 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Champix 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets. Champix 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 Varenicline CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 January 2025.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5189/001-3/IB/003	Change in test procedure for the finished product - Minor changes to an approved test procedure	No	24-09-2025	Approved	N.A.
NL/H/5189/001-3/IA/005	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) - Change that affects the product information	Yes	02-10-2025	Approved	N.A.
NL/H/5189/001-3/IB/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products - Other variation: Correction of typographical error outer packaging and update of SmPC and PL	Yes	26-10-2025	Approved	N.A.