COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Varenicline Teva 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets (varenicline citrate)

NL/H/5740/001-003/DC

Date: 26 November 2025

This module reflects the scientific discussion for the approval of Varenicline Teva 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets. The procedure was finalised on 29 February 2024. 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 Teva 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets, from Teva 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 Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Luxembourg, Norway, Portugal, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Varenicline Teva 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 Teva 0.5 mg
White, capsule-shaped (8 mm x 4 mm) film-coated tablet, debossed with '0.5' on one side. Each tablet contains as active substance 0.5 mg of varenicline, as varenicline citrate.

Varenicline Teva 1 mg
Light blue, capsule-shaped (10 mm x 5 mm) film-coated tablet, debossed with '1.0' on one side. Each tablet contains as active substance 1 mg of varenicline, as varenicline citrate.

The excipients are:
Tablet core - cellulose, microcrystalline (E460); pregelatinised starch (maize starch); magnesium stearate (E470b), propyl gallate (E310) and citric acid (E330).
Film-coating 0.5 mg tablet - hypromellose (E464) and titanium dioxide (E171).
Film coating 1 mg tablet: - hypromellose (E464), titanium dioxide (E171) and indigo carmine aluminium lake (E132).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in either:

- polyvinyl chloride/polyethylene/polyvinylidene chloride//aluminium (PVC/PE/PVdC//Alu) blisters. Applies to the 1.0 + 0.5 mg strength.
- polyvinyl chloride/polyethylene/polyvinylidene chloride//aluminium (PVC/PE/PVdC//Alu) perforated unit dose blisters.
  Applies to the 0.5 mg and 1.0 mg strengths.
- high-density polyethylene (HDPE) bottle (with polypropylene child-resistant closure).
  Applies to the 0.5 mg and 1.0 mg strengths

II.2 Drug Substance

The active substance is varenicline citrate, an active substance not described in any compendial monograph. The active substance is an off white/beige to light orange powder. It is very soluble in dimethyl sulfoxide and dimethyl formamide, freely soluble in water and practically insoluble in methanol, ethanol, hexane, diethyl ether, petroleum ether, acetonitrile, acetone, dichloromethane and toluene. Varenicline has no stereoisomers. The active substance varenicline citrate is a salt formed by varenicline free base and citric acid. For this product, polymorphic form A is consistently produced.

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 a six step synthesis, followed by filtration, drying and sieving. 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 has been established in-house by the applicant as there is no compendial monograph available that describes the active substance. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated conditions.

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 formulation composition was finalised based on formulation development trials. Reformulation was needed because of risk for the formation of nitrosamines identified in a risk assessment of an earlier formulation. After reformulation of the drug product, the manufacturing process was changed. The development and risk assessment of the updated manufacturing process are provided. Comparative dissolution testing at three pHs has been successfully studied in support of the bioequivalence study (with 1 mg product) and the biowaiver of strength for the old formulation. The reformulated drug products may be considered similar to the batches of the old formulation (and thus to the reference product) as the dissolution profiles are similar in all pHs.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process concerns a wet granulation method involving sifting, dry mixing, granulation, drying, milling, (blending for) compaction, lubrication, compression, coating and packing. The manufacturing process is considered to be a non-standard pharmaceutical dose form because it concerns a unit dose product containing drug substance in low content (≤2% of composition).

Process validation data on the product have been presented for two batches (smallest commercial scale and largest commercial scale) in accordance with the relevant European guidelines.

Control of excipients

Microcrystalline cellulose, pregelatinised starch (maize starch), magnesium stearate, propyl gallate, anhydrous citric acid, anhydrous ethanol, purified water, hypromellose 2910 (6mPas) and titanium dioxide comply with Ph. Eur. requirements. Indigo carmine aluminium lake complies with the EU Regulation 231/2012. Justification is provided for not including testing for functionality related characteristics. 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 appearance, identification, water content, dissolution, uniformity of dosage units, IM2 impurity content, residual solvent, related substances and microbiological quality. 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 nitrosamine impurity SM3 can be a potential by-product of nitration reaction. Data is submitted to support

that SM3 shows values significantly below the 10% threshold of applicable limit as 13 samples of API show SM3 impurity is below limit of detection (<4 ppb). A test for this impurity is therefore not necessary.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from six commercial scaled batches (three of each strength) from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches for each strength stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months). in accordance with applicable European guidelines. Photostability studies showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 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 Teva 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 Teva 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 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 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 Teva 1 mg, film-coated tablets (Teva B.V., the Netherlands) of the old formulation 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.

Biowaiver

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

a. The 0.5 mg and 1.0 mg strengths are manufactured by the same process.
b. The qualitative composition of the two strengths is the same.
c. The composition of the two strengths is 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.

Dissolution profiles of the two strengths at pH 1.2, 4.5 and 6.8, using acceptable dissolution conditions, can be accepted as similar, given that >85% was dissolved within 15 minutes. The dissolution of the 0.5 mg strength and 1 mg strength was investigated according to the EMA Bioequivalence guideline. The calculated f2 similarity factor values, at three pH values (pH 1.2, pH 4.5 and pH 6.8), were within criteria (>50%). An f2 value between 50 and 100% suggests that the dissolution profiles of the two compared dissolution profiles are similar.

Therefore, in case the nitrosamines would not have been an issue, a biowaiver could have been granted for the 0.5 mg strength of the test product. However, the product has been reformulated because of an issue with nitrosamines. No new bioequivalence study is considered necessary because:

- The excipients that have been added to the formulation are not expected to affect the

absorption of varenicline and the total changes are small (<5%).

- The absorption of varenicline is well over 90% (Faessel *et al.* Eur J Clin Pharmacol 2008).
- Very rapid dissolution (>85% within 15 minutes) was observed at both strengths for both test formulations and reference products at pH 1.2, 4.5 and 6.8 because of the high solubility of varenicline salts.

Therefore, the reformulated test product can still be considered bioequivalent to the reference product.
Hence, a biowaiver can be granted for the 0.5 mg and 1 mg strength of the reformulated test product.

Bioequivalence study

Design

An open label, single-dose, randomised, two-period, two-way crossover bioequivalence study was carried out under fasted conditions in 28 healthy male (13) and female (15) subjects, aged 19-48 years. Each subject received a single dose (1 mg) of one of the two varenicline formulations. The tablet was orally administered with 240 ml water after a fasting period of at least ten hours. There were two dosing periods, separated by a washout period of ten days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 12, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

The design of the study is acceptable.

Varenicline may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of varenicline. 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

One subject was dropped out in period 1 due to emesis within seven hours from drug administration. 27 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=27	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	127487 ± 23991	129993 ± 24298	6119 ± 1123	2.50 (0.50-4.33)
Reference	131433 ± 28860	131407 ± 29365	5842 ± 1224	2.50 (1.50-7.00)
***Ratio (90% CI)**	0.98 (0.91-1.06)	0.98 (0.91-1.06)	1.06 (0.99-1.12)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
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 Teva 1 mg, film-coated tablets (old formulation) is considered bioequivalent with Champix 1 mg, film-coated tablets. However, the product has been reformulated because of an issue with nitrosamines. No new bioequivalence study is considered necessary. The reformulated test product can still be considered bioequivalent to the reference product.

The results of the study with the 1 mg strength can be extrapolated to the other strength 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 Teva. At the time of approval, the most recent version of the RMP was version 1.0 dated 12 December 2022.

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. No new clinical studies were conducted. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Champix 0.5 mg, 1 mg and 0.5 mg + 1 mg, film-coated tablets (EMEA/H/C/000699) for key safety messages and text content of common package leaflet and to Capecitabin Tiefenbacher 500 mg, film-coated tablets (FR/H/0589/001-002/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Varenicline Teva 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 Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 February 2024.

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/5740/001-3/IA/001	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product -Secondary packaging site	No	26-6-2024	Approved	N.A.
NL/H/5740/003/IB/002	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products -Other variation	Yes	11-12-2024	Approved	N.A.
NL/H/5740/001-3/IB/003/G	Changes in the manufacturing process of the active substance - Minor change to the restricted part of an Active Substance Master File. Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Tightening of specification limits Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Minor changes to an approved test procedure	No	7-1-2025	Approved	N.A.
NL/H/5740/001/IA/004	Change to importer, batch release arrangements and quality control testing of the finished product	Yes	27-1-2025	Approved	N.A.

	- Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
NL/H/5740/001-3/WS/005	Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	Yes	19-7-2025	Approved	N.A.