COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ivabradine Teva 5 mg and 7.5 mg, film-coated tablets (ivabradine hydrochloride)

NL/H/5568/001-002/DC

Date: 17 March 2026

This module reflects the scientific discussion for the approval of Ivabradine Teva 5 mg and 7.5 mg, film-coated tablets. The procedure was finalised on 5 June 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 Ivabradine Teva 5 mg and 7.5 mg, film-coated tablets, from Teva B.V.

The product is indicated for:
Symptomatic treatment of chronic stable angina pectoris
Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated:

- in adults unable to tolerate or with a contraindication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Treatment of chronic heart failure
Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in adult patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

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 Procoralan 5 and 7.5 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/05/316/001-007 and EU/1/05/316/008-014) by Les Laboratoires Servier Industrie since 25 October 2005 and 28 October 2005.

The concerned member states (CMS) involved in this procedure was France.

II. QUALITY ASPECTS

II.1 Introduction

Ivabradine Teva is a film-coated tablet. The two different strengths can be distinguished by their appearance, based on their shape and debossing, as follows:

Ivabradine Teva 5 mg
White or almost white, oval, biconvex, film-coated tablet, marked with "A274" on one side and score on the other side.
Each film-coated tablet contains 5 mg ivabradine (as hydrochloride).

Ivabradine Teva 7.5 mg
White or almost white, triangular, biconvex, film-coated tablet, marked with "A267" on one side.
Each film-coated tablet contains 7.5 mg ivabradine (as hydrochloride).

The excipients are:
Tablet core - magnesium stearate (E470b), colloidal anhydrous silica (E551), maltodextrin, maize starch and lactose monohydrate.

Film-coating - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521) and talc (E553b).

The core tablets composition is fully proportional between the two strengths.

The film-coated tablets are packed in oriented polyamide (OPA)-Aluminium-polyethelyne (PE)-Desiccant/Aluminium- polyethylene (PE) blister packs. The desiccant calcium oxide (CaO) is embedded in a polyolefin sealant layer. Multi-layered foil does not allow contact between desiccant and tablets. The blisters are packed in cardboard boxes.

II.2 Drug Substance

The active substance is ivabradine hydrochloride, an established active substance not described in any Pharmacopoeia. The active substance is soluble in water (across pH 1.2 to 7.4) and methanol, and practically insoluble in tetrahydrofuran. The drug substance contains one chiral centre; hence it exists as two isomers: R and S. Ivabradine HCl exists in several different polymorphic forms. For this product, the same polymorphic form 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 the synthesis of two intermediates, followed by five stages. No class 1 solvents are intentionally added. 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 has been established by the MAH. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance

Stability data on the active substance have been provided for nine batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 18 months 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 choice of excipients is justified and their functions explained. The choice of the manufacturing process, i.e., the fluid bed granulation method, has been adequately justified.

Manufacturing process

The main manufacturing steps are screening, granulation, drying, screening, blending, compression, film coating and blister packing. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for eight commercial scale batches per strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. The components of the film-coating are complying with current edition of European Pharmacopoeia. The functionality related characteristics have been included to the specification of excipients, where applicable. 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, identification, average mass, uniformity of dosage units, subdivision of tablets (only for the 5 mg strength), dissolution, disintegration, assay, degradation product and microbial limits. 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. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from two pilot scaled batches per strength manufactured at site I and five commercial scaled batches per strength manufactured at site II have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches per strength manufactured at site II, stored at 25°C/60% RH (24-36 months), 30°C/75% RH (24-36 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. 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

Scientific data and/or certificates of suitability issued by the EDQM for excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ivabradine 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 Ivabradine 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 Procoralan 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

Ivabradine hydrochloride 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. In addition, the MAH requested a biowaiver for the lower 5 mg strength.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivabradine Teva 7.5 mg, film-coated tablets (Teva B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Procoralan 7.5 mg, film-coated tablets (Les Laboratoires Servier Industrie, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The dissolution profiles of the strengths are considered similar, given that the mean dissolution is >85% after 15 minutes in all cases in 0.1M HCl, pH 4.5 and pH 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

<u>Biowaiver</u>
Bioequivalence studies were not carried out on all strengths, since all conditions listed in section 4.1.6 of the Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1 are fulfilled for the additional strength compared to the tested strength.
The following requirements for a biowaiver for the 5 mg strength of the test product were met:

a. all strengths are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. 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,

d. comparative dissolution profiles across the physiological pH range indicate that the dissolution profiles are similar when compared between the strengths.

The dissolution was investigated according to the EMA Bioequivalence guideline. The dissolution profiles of the strengths are considered similar, given that the mean dissolution is >85% after 15 minutes in all cases in 0.1M HCl, pH 4.5 and pH 6.8.

Therefore, a biowaiver for the 5 mg strength of the test product can be granted, given that bioequivalence was shown with the 7.5 mg strength.

Bioequivalence study

Design

A single-dose, randomised, three-period, three-treatment, six-sequence, crossover bioequivalence study was carried out under fed conditions in 30 healthy male subjects, aged 21-39 years. Each subject received a single dose (7.5 mg) of one of the three ivabradine formulations. The tablet was orally administered with 240 ml water 30 minutes after an high calorie high fat breakfast (979 kcal). There were three dosing periods, separated by a washout period of five days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30%. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure.

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 dropped out after period I, because he did not check-in for period II of the study. Of the 30 subjects enrolled in the study, 29 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ivabradine, 7.5 mg under fed conditions.

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test A	269 ± 106	274 ± 110	53 ± 22	2.00 (1.00 - 5.00)
Test B	259 ± 97	264 ± 100	48 ± 15	2.00 (0.50 - 4.50)
Reference	250 ± 98	255 ± 102	47 ± 20	2.33 (0.50 - 4.00)
***Ratio (90% CI) A/C**	1.07 (1.02 - 1.12)	1.07 (1.02 - 1.12)	1.14 (1.07 – 1.22)	-
***Ratio (90% CI) B/C**	1.05 (1.01 - 1.10)	1.05 (1.01 - 1.10)	1.05 (0.98 – 1.13)	-

$AUC_{0-\infty}$	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 = 24 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 Ivabradine Teva 7.5 mg is considered bioequivalent with Procoralan, 7.5 mg.

The results of the bioequivalence study with the 7.5 mg formulation can be extrapolated to the lower strength of 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 Ivabradine Teva. At the time of approval, the most recent version of the RMP was version 3.0 dated 2 August 2022.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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 Procoralan. 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 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

Ivabradine Teva 5 mg and 7.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Procoralan 5 and 7.5 mg, film-coated tablets. Procoralan 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 Ivabradine Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 June 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/5568/001-002/WS/003	Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms. Change in container closure system of the Finished Product - Other variation.	Yes Yes	20-03-2025	Approved	N.A.
NL/H/5568/001-002/WS/001	Type II: B.I.z - update ASMF.	N.A.	31-08-2025	Refused	The information provided in the restricted part of the ASMF is not sufficient to support the application for variation.
NL/H/5568/001-002/WS/002	Change in the manufacturer of a starting material/reagent /intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the	No	09-09-2025	Approved	N.A.

	approved dossier - Introduction of a manufacturer of the active substance supported by an ASMF.				