CBG MEB

Public Assessment Report

Scientific discussion

Ivabradine Chanelle Medical 5 mg and 7.5 mg film-coated tablets

(ivabradine oxalate)

NL/H/3645/001-002/DC

Date: 8 January 2018

This module reflects the scientific discussion for the approval of Ivabradine Chanelle Medical 5 mg and 7.5 mg film-coated tablets. The procedure was finalised on 10 November 2016. 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
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
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 Chanelle Medical 5 mg and 7.5 mg film-coated tablets from Chanelle Medical.

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 contra-indication 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 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Procoralan 5 mg and 7.5 mg film-coated tablets which have been registered in the EEA by Les Laboratoires Servier since 25 October 2005 through a centralised procedure (EU/1/05/316).

The concerned member states (CMS) involved in this procedure were Germany, France, Ireland, Poland, Portugal, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Ivabradine Chanelle Medical 5 mg is a salmon coloured, oblong shaped, biconvex film-coated tablet with a breakline on one side and plain on the other. The tablet can be divided into equal doses. One film-coated tablet contains 5 mg ivabradine (equivalent to 5.96 mg ivabradine oxalate).

Ivabradine Chanelle Medical 7.5 mg is a salmon coloured, triangular shaped, biconvex, film-coated tablet plain on both sides. One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.94 mg ivabradine oxalate).

The film-coated tablets are packed in blisters (composed of rigid clear transparent PVC film coated with PCTFE clear and Aluminium Foil).

The excipients are:
Core - microcrystalline cellulose (E460), crospovidone, Type A (E1202), colloidal anhydrous silica (E551), hydrogenated castor oil,

Film-coating -
Opadry orange - hypromellose (E464), microcrystalline cellulose (E460), titanium dioxide (E171), stearic acid (E570), yellow iron oxide (E172), red iron oxide (E172)

Polishing Agent - carnauba wax

The two strengths are fully dose proportional.

II.2 Drug Substance

The active substance is ivabradine oxalate, an established active substance however not described in any pharmacopoeia. It is a white to off white, hygroscopic powder, which is soluble in chloroform and sparingly soluble in methylene chloride. The substance exhibits chirality (1 chiral centre is present). Ivabradine oxalate exists as S-isomer & R-isomer. The S-isomer is used and the R-isomer is regarded as an impurity and controlled in the drug substance specification. Ivabradine oxalate can exist in various polymorphic forms. The crystalline form is 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 starting materials are non-complex substances. Therefore, the choice of the starting materials and the applied specifications are considered acceptable. The manufacturing process is sufficiently described.

Quality control of drug substance
Adequate drug substance specifications have been laid down. The MAH applies drug substance specifications which are in line with those from the ASMF holder, except the particle size distribution. The analytical methods have been sufficiently described and adequately validated. Batch analysis data have been provided with results meeting the set drug substance specification, including data from four re-crystallized batches to achieve the desired particle size.

Stability of drug substance
Three batches of drug substance have been put on stability for 12 months at 25°C/60% RH and 6 months at 40°C/75% RH. In addition data are available from batches produced by a different manufacturing process, a recrystallized drug substance batch and batches using an intermediate stage.
All intermediate and long-term stability results show that the drug substance specifications are met. At accelerated conditions, an increase in one impurity was observed. Therefore, the storage condition of ivabradine oxalate has been established as "Store in a well closed container at a temperature not exceeding 25°C". The results support the claimed shelf life of 36 months.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development studies include optimization of formulation and process variables and comparative dissolution studies with the reference product. The proposed products and the reference product contain the same amounts of the same active moiety and concern the same pharmaceutical form. Due to patent reasons the MAH chose to use ivabradine oxalate instead of ivabradine hydrochloride, which is present in the innovator. Comparative data on physicochemical characteristics, solubility at different pHs, and hygroscopicity of ivabradine hydrochloride and ivabradine oxalate were presented. The choice for ivadrabine oxalate has been sufficiently justified.

A bioequivalence study was performed by comparing the 7.5 mg test product to Procoralan 7.5 mg. Comparative *in vitro* dissolution data support bioequivalence. The justification given for waiving the bioequivalence of the 5 mg strength is considered acceptable. Dissolution profiles of the two strengths were similar at three pH values; the dissolution was more than 85% within 15 min for both products.. The subdivision of the 5 mg strength is in accordance with the Ph. Eur. requirements.

Manufacturing process
The drug product is prepared by a conventional direct compression process followed by film-coating. The process is a standard manufacturing process. Relevant process parameters are included in the description of the manufacturing process. Process validation has been performed on three blend batches and on three tablet batches per strength on pilot scale. Process validation will be conducted on commercial scale batches prior to marketing.

Control of excipients
The excipients comply with Ph. Eur. Requirements, except for Opadry Orange, which complies with in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identity of ivabradine and colourants, uniformity of mass, assay, uniformity of dosage units by content uniformity, disintegration time, subdivision of tablets (5 mg only), dissolution, impurities (including R-isomer), and microbiological quality. Batch analysis data have been provided for six validation batches, three for each strength, including the biobatch. The results are consistent and comply with the proposed specifications.

Stability of drug product
Stability studies at accelerated (40°C/75% RH, 6 months) conditions are available for three batches per strength in the primary packaging material, and data at long-term conditions (25°C/60% RH, 24 months) are available for two batches per strength in the primary packaging material. A third batch has been put in the stability program and 6 months data have been provided. The results comply with the specifications. A photostability study in line with ICH Q1B confirms that the product is photostable.
Based on the stability data, a shelf-life of 36 months can be granted, without special storage conditions.

Specific measures for 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 Ivabradine Chanelle Medical 5 mg and 7.5 mg have 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 Chanelle Medical is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is 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 is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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 is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted 2 bioequivalence studies: a pilot study to estimate the variability in the pharmacokinetic variables and a pivotal bioequivalence study with the highest dose under fed conditions.

IV.2 Pharmacokinetics

A pilot study was conducted to estimate the intra-individual variability and the optimal sampling scheme. This study was conducted in 12 subjects. This pilot study showed a low variability and the 90% confidence intervals were within the acceptance criteria for bioequivalence. Only the pivotal study is further described below. The pilot study did not show contradictory data compared with the pivotal study.

In the pivotal bioequivalence study the pharmacokinetic profile of the test product Ivabradine Chanelle Medical 7.5 mg (Chanelle Medical, Ireland) was compared with the pharmacokinetic profile of the reference product Procoralan 7.5 mg film-coated tablets (Les Laboratoires Servier, France).

The choice of the reference product in the bioequivalence study is justified as Procoralan has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The 5 mg and 7.5 mg strengths are dose-proportional and are manufactured by the same manufacturing site using the same manufacturing process. The pharmacokinetics of ivabradine are linear. Dissolution tests at pH 1.2, 4.5 and 6.8 showed comparable dissolution, i.e. more than 85% within 15 minutes. The biowaiver for the 5 mg tablet is considered acceptable.

Bioequivalence studies
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 26 healthy male subjects, aged 21-43 years. The subjects fasted for at least 10 hours prior to the start of the breakfast. Subjects consumed a breakfast starting 30 minutes prior to drug administration. Subjects consumed a breakfast starting 30 minutes prior to drug administration. The breakfast consisted 2 eggs, 14 g of butter,, 60 g slices bread, 110 g of hash brown potatoes, 250 ml of whole milk and 60 g chicken. Total caloric content was about 1000 kcal.
Each subject received a single dose (7.5 mg) of one of the 2 ivabradine formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.167, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. The blood sampling scheme is adequate, and the wash-out period long enough regarding the half life of 11 hours. As the product should be administered with food, the choice of a high fat, high caloric meal is acceptable.

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
Twenty four subjects completed the study and were included in the pharmacokinetic analysis. One subject was withdrawn due to adverse events and one subject did not report for the second period.

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	148 ± 40.6	151 ± 42.4	30.1 ± 10.6	2.1 0.5 - 5.0	--
Reference	147 ± 45.9	149 ± 46.6	34.3 ± 15.5	1.25 0.75 - 5.0	--
***Ratio (90% CI)**	1.02 (0.96 - 1.09)	--	0.91 (0.81 - 1.02)	--	--
CV (%)	12.7	--	23.1	--	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ivabradine Chanelle Medical 7.5 mg is considered bioequivalent with Procoralan 7.5 mg film-coated tablets.

Safety
No serious adverse events were reported during the conduct of this study. The study medications were well tolerated by the healthy volunteers that participated in this study.

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 Chanelle Medical.

Summary of safety concerns	
Important identified risks	Bradycardia
	Phosphenes/blurred vision
	2nd and 3rd degree Atrioventricular blocks
	Increase in blood pressure in hypertensive patients
	Atrial fibrillation (AF)
	ECG prolonged QT interval
Important potential risks	Supra-ventricular tachyarrhythmia (SVT) other than AF
	Immune disorders
	Severe ventricular arrhythmia
	Myocardial infarction
Missing information	Children and adolescents (< 18 years old)
	Pregnant and lactating women
	Severe hepatic insufficiency
	Severe renal impairment
	Chronic heart failure patients with intra-ventricular conduction defects

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. 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

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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. There were seventeen questions about the most critical parts of the package leaflet and four general questions about the package leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The package leaflet has not been adapted between the two main rounds. No adaptations have been made after the last test.
Taking into account the results for each question more than 90% of the participants were able to find the section and answer the question correctly. 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

Ivabradine Chanelle Medical 5 mg and 7.5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Procoralan 5 mg 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 Chanelle Medical with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 10 November 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached