CBG MEB

# Public Assessment Report

# Scientific discussion

# Ivabradine Bristol 5 mg and 7.5 mg film-coated tablets

# (ivabradine hydrochloride)

# NL/H/3694/001-002/DC

# Date: 7 May 2018

**This module reflects the scientific discussion for the approval of Ivabradine Bristol 5 mg and 7.5 mg film-coated tablets. The procedure was finalised on 13 June 2017. 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 |
| 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 Bristol 5 mg and 7.5 mg film-coated tablets from Bristol Laboratories Ltd (Berkhamsted).

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 (see SmPC section 5.1).

A comprehensive description of the indications and posology is given in the SmPC.

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 has been registered in the EEA by Les Laboratoires Servier through a centralised procedure (EU/1/05/316/001-0014) since 25 October 2005.

The concerned member states (CMS) involved in this procedure were Germany 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 Bristol is a film-coated tablet:

- The 5 mg strength is a salmon coloured, oval shape, biconvex, film-coated tablet scored on both sides, engraved with ´5´ at one side, plain on the other side. The tablet can be divided into two equal doses.
- The 7.5 mg strength is a salmon coloured, triangular, biconvex, film-coated tablet, engraved with ´7.5´ at one side and plain on the other side.

The product contains as active substance 5 mg or 7.5 mg of ivabradine, as 5.39 mg or 8.085 mg of ivabradine hydrochloride.

The film-coated tablets are packed in Aluminium/Aluminium blisters.

The excipients are:
*Tablet core* - microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica and, magnesium stearate.
*Film-coating* - Opadry Orange 03F230017 containing hypromellose 6cp, titanium dioxide (E171), macrogol 6000, magnesium stearate, glycerol, iron oxide red (E172) and iron oxide yellow (E172)

The two tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is ivabradine hydrochloride, an established active substance that is not described in any Pharmacopoeia. Ivabradine hydrochloride is a white to slightly yellow powder, soluble in methanol and water. It is a chiral compound and possesses one asymmetric carbon atom. Ivabradine hydrochloride displays polymorphism. The drug substance manufacturing process results in polymorphic form II.

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 of ivabradine hydrochloride consists of five consecutive stages. The information provided on the manufacturing process is acceptable. The two starting materials are acceptable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
Stability data on the active substance have been provided for six batches, which have been stored at long-term (60 months) and accelerated conditions (6 months). Ivabradine hydrochloride is generally very stable at both conditions and no specific degradation trends are being observed. No increase in water content is observable over time. However, two batches give out-of-specification results for the polymorphic form II after 24 months of long-term testing. No change in the polymorphic form is observed under accelerated storage conditions. Based on the provided stability data, the re-test period of 18 months with the storage condition "Store the material under nitrogen in tightly closed container with molecular sieve at a temperature below 25°C" is acceptable.

## 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 excipients are well known and their use justified. The product is intended as an immediate release product. Breakability of the 5 mg tablets was adequately demonstrated. The tablet can be divided into two equal doses.

One bioequivalence study has been submitted comparing the 7.5 mg strength with the innovator product. The dissolution characteristics of the 7.5 mg test product were also compared to the innovator Procoralan. The release characteristics were determined in 900 ml of dissolution medium (0.1N HCl, phosphate buffer pH 4.5 and phosphate buffer pH 6.8). Both products dissolve rapidly and complete dissolution is obtained after 15 minutes.

The MAH applied for a biowaiver for the lower 5 mg strength. Both strengths of the test product show dissolution greater 85% within 15 minutes in the release media 0.1N HCl and phosphate buffers at pH 4.5 and 6.8, without the addition of a surfactant.

Manufacturing process
The manufacturing process is a standard process and has been described in sufficient detail. It is a simple direct compression, followed by film-coating of the cores. 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 in accordance with the relevant European guidelines.

Control of excipients
All excipients are commonly used in medicinal products and comply with their respective monographs in the Ph.Eur., except for Opadry Orange. The specification for the Opadry coating is included and all components comply with the Ph.Eur., except for iron oxides red and yellow, which comply with the Directive 95/45/EC. 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 of the active substance, identification of colouring, dimensions, average weight, uniformity of dosage units, water content, assay, dissolution, disintegration, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Six batches of Ivabradine film-coated tablets (three batches of each strength) were included in the stability study. The MAH submitted stability data up to 24 months long term and six months accelerated conditions for tablets of each strength. The results were not out of specification. Based on the provided stability data, the proposed shelf-life and storage condition '24 months shelf-life with no special storage conditions for the finished product in Al/Al blisters. Store in the original packaging to protect from moisture' is acceptable. The drug product is not considered to be photosensitive.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose, employed in the tablet core, is of bovine origin. Scientific data and/or certificates of suitability issued by the EDQM 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 Bristol 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 Bristol 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 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 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 one bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivabradine Bristol 7.5 mg film-coated tablets is 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*
The choice of the reference product in the bioequivalence study has been justified as it is the European reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Biowaiver*
A biowaiver for the 5 mg film-coated tablets strength is justified based on the following:

- The 5 mg strength is manufactured by the same manufacturing process as the 7.5 mg strength.
- The qualitative composition of the different strengths is the same.
- The ratio between amounts of active substance and excipients is the same.
- Pharmacokinetics are linear over the therapeutic dose range.
- The *in vitro* dissolution profile is similar under identical conditions for all strengths. Comparative dissolution testing was performed at three pH conditions. Similarity between the 7.5 mg biobatch and the 5 mg strengths was shown at pH 1.2, 4.5 and 6.8 as more than 85% of the drug was dissolved within 15 minutes.

*Design*
A randomised, open-label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 60 healthy male (n=48) and female (n=12) subjects, aged 18-44 years. Each subject received a single dose (7.5 mg) of one of the two ivabradine formulations. The tablet was orally administered with 240 ml water. All subjects fasted overnight for at least 10 hours. The subjects received breakfast (approximately 800 to 1000 calories) 30 minutes prior to administration of the reference or test drug. There were two dosing periods, separated by a washout period of nine days.

Blood samples were collected at pre-dose (1 hour) and post-dose at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 11, 14, and 24 hours after administration of the products.

The design of the study is acceptable. The wash-out period was was more than five half-lives of ivabradine (elimination half-life is two hours), which is long enough to prevent carry-over effects. Furthermore, the sampling period was long enough and the sampling scheme was adequate to estimate the pharmacokinetic parameters. The fed condition is in accordance with the SmPC.

*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 did not report for dosing in period 2 and were therefore not included in the statistical analysis. In addition, one subject reported adverse event in period 2 before dosing and was therefore withdrawn from the study. Therefore, 57 subjects were eligible for pharmacokinetic analysis.

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

| **Treatment N=57** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 146.7 ± 69.1 | 152.9 ± 68.2 | 30.9 ± 14.3 | 1.75 (0.5 - 6.0) |
| **Reference** | 139.3 ± 65.1 | 142.6 ± 66.2 | 29.8 ± 14.1 | 1.75 (0.5 - 4.0) |
| ***Ratio (90% CI)** | 1.07 (1.02 - 1.11) | 1.07 (1.02 - 1.11) | 1.05 (0.97 - 1.12) | -- |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration | | | | |

**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 Bristol 7.5 mg film-coated tablets is considered bioequivalent with Procoralan 7.5 mg film-coated tablets.

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 Bristol.

Summary table of safety concerns as approved in RMP:

| | |
|---|---|
| Important identified risks | • Bradycardia<br>• Phosphenes/blurred vision<br>• Atrioventricular (AV) block 2nd and 3rd degree<br>• Increase in blood pressure in hypertensive patients<br>• Atrial fibrillation (AF)<br>• Prolonged QT interval on electrocardiogram (ECG) |
| Important potential risks | • Supra-ventricular tachyarrhythmia (SVT) other than AF<br>• Immune disorders<br>• Myocardial infarction<br>• Severe ventricular arrhythmia |
| Missing information | • Children and adolescents (<18 years old)<br>• Pregnant and lactating women<br>• Severe hepatic insufficiency<br>• Severe renal impairment<br>• 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

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 Procoralan and the lay-out of a different approved, user tested medicinal product of the same Marketing Authorisation Holder. 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

Ivabradine Bristol 5 mg and 7.5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form 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 Bristol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 June 2017.

## 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 |
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