



## **Public Assessment Report**

### **UKPAR**

**Ivabradine 5 mg film-coated tablets  
Ivabradine 7.5 mg film-coated tablets**

**(Ivabradine hydrochloride)**

**UK Licence Number: PL 12762/0541-0542**

**Mercury Pharmaceuticals Limited.**

## LAY SUMMARY

Ivabradine 5 mg film-coated tablets  
Ivabradine 7.5 mg film-coated tablets

(Ivabradine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Ivabradine 5 mg film-coated tablets (PL 12762/0541) and Ivabradine 7.5 mg film-coated tablets (PL 12762/0542). It explains how Ivabradine 5 mg and 7.5 mg film-coated tablets were assessed and why authorisation was recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Ivabradine 5 mg and 7.5 mg film-coated tablets.

The products will be collectively referred to as 'Ivabradine' throughout the remainder of this PAR.

For practical information about using Ivabradine, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Ivabradine and what is it used for?**

Ivabradine is a 'generic medicine'. This means that Ivabradine is similar to a 'reference medicine' already authorised in the EU called Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier).

Ivabradine is a heart medicine used to treat:

- Symptomatic stable angina pectoris (which causes chest pain) in adult patients whose heart rate is over or equal to 70 beats per minute. It is used in adult patients who do not tolerate or cannot take heart medicines called beta-blockers. It is also used in combination with beta-blockers in adult patients whose condition is not fully controlled with a beta-blocker.
- Chronic heart failure in adult patients whose heart rate is over or equal to 75 beats per minute. It is used in combination with standard therapy, including beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.

**About stable angina pectoris (usually referred to as "angina"):**

Stable angina is a heart disease which happens when the heart does not receive enough oxygen. It usually appears between 40 and 50 years of age. The most common symptom of angina is chest pain or discomfort. Angina is more likely to happen when the heart beats faster in situations such as exercise, emotion, exposure to the cold or after eating. This increase in heart rate can cause the chest pain in people who suffer from angina.

**About chronic heart failure:**

Chronic heart failure is a heart disease which happens when the heart cannot pump enough blood to the rest of the body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

**How does Ivabradine work?**

This medicine contains the active ingredient ivabradine hydrochloride which mainly works by reducing the heart rate by a few beats per minute. This lowers the heart's need for oxygen especially in the situations when an angina attack is more likely to happen. In this way Ivabradine helps to control and reduce the number of angina attacks.

Furthermore, as elevated heart rate adversely affects the heart functioning and vital prognosis in patients with chronic heart failure, the specific heart rate lowering action of ivabradine helps to improve the heart functioning and vital prognosis in these patients.

**How is Ivabradine used?**

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are unsure.

Ivabradine should be taken during meals.

**For patients being treated for stable angina pectoris**

The starting dose should not exceed one tablet of Ivabradine 5 mg twice daily. If the patient still has angina symptoms and if they have tolerated the 5 mg twice daily dose well, the dose may be increased. The maintenance dose should not exceed 7.5 mg twice daily. The patient's doctor will prescribe the right dose for them.

The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if the patient is elderly), the patient's doctor may prescribe half the dose i.e., one half of a 5 mg tablet of Ivabradine 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half of a 5 mg tablet in the evening.

**For patients being treated for chronic heart failure**

The usual recommended starting dose is one tablet of Ivabradine 5 mg twice daily, increasing if necessary to one tablet of Ivabradine 7.5 mg twice daily. The patient's doctor will decide the right dose for them.

The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if the patient is elderly), the patient's doctor may prescribe half the dose i.e., one half of a 5 mg tablet of Ivabradine 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half of a 5 mg tablet in the evening.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Ivabradine is used, refer to the package leaflet and Summaries of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Ivabradine can only be obtained with a prescription.

**What benefits of Ivabradine have been shown in studies?**

Because Ivabradine is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier). Two medicines are considered to be bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Ivabradine?**

Ivabradine is a generic medicine and is bioequivalent to the reference medicine Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier) so the benefits and possible side effects are taken as being the same as for the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Ivabradine, see section 4 of the package leaflet available on the MHRA website.

**Why was Ivabradine approved?**

It was concluded that, in accordance with EU requirements, Ivabradine has been shown to have

comparable quality and to be bioequivalent to Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier). Therefore, the MHRA decided that, as for Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier), the benefits are greater than the risks and recommended that they can be approved for use.

**What measures are being taken to ensure the safe and effective use of Ivabradine?**

A risk management plan (RMP) has been developed to ensure that Ivabradine is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for Ivabradine including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Ivabradine**

Marketing Authorisations were granted in the UK on 15 October 2018.

The full PAR for Ivabradine follows this summary.

For more information about treatment with Ivabradine, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

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## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Mercury Pharmaceuticals Limited, a marketing authorisation for the medicinal product Ivabradine (PL 12762/0541-0542) on 15 October 2018.

Ivabradine is a prescription only medicine (POM) 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  $\geq 70$  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  $\geq 75$  bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Procoralan 5mg and 7.5mg film-coated tablets which were first authorised to Les Laboratoires Servier (Marketing Authorisation Numbers: EU/1/05/316/003 and EU/1/05/316/010) on 27 October 2005 via the Centralised procedure.

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker  $I_f$  current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also with the retinal current  $I_h$  which closely resembles cardiac  $I_f$ . It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of  $I_h$  by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.

One bioequivalence study (single-dose study conducted under fed conditions) was submitted to support these applications. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Ivabradine outweigh the risks and Marketing Authorisations was granted.

## II QUALITY ASPECTS

### II.1 Introduction

Each film-coated tablet contains 5 mg or 7.5 mg of ivabradine (as hydrochloride) as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

#### Core

Anhydrous lactose, maltodextrin, crospovidone type A, colloidal anhydrous silica and magnesium stearate

#### Coating

Coating medium consisting of:

Hypromellose, polydextrose, titanium dioxide (E171), talc, maltodextrin/dextrin, medium chain triglycerides, iron oxide yellow (E172) and iron oxide red (E172).

The finished product is packaged in OPA/AL/PVC- Aluminium foil blisters (Alu-Alu blisters) packed in a cardboard carton and are available in calendar packs containing 28, 56 or 98 film-coated tablets. Not all pack sizes may be marketed.

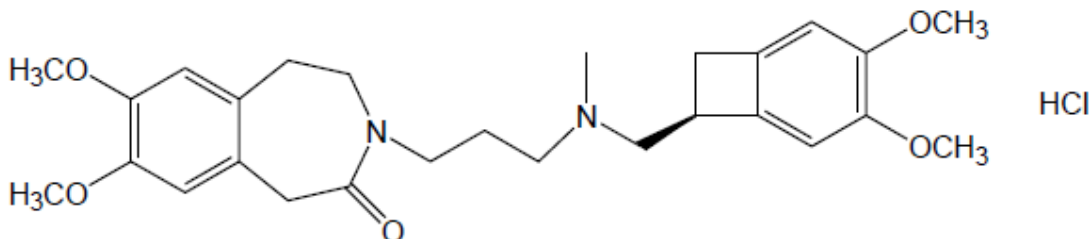
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

### II.2 Drug Substance

INN: Ivabradine hydrochloride

Chemical name: 2*H*-3-Benzazepin-2-one, 3-[3-[[[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-, hydrochloride (1:1)

Structure:



Molecular formula: C<sub>27</sub>H<sub>37</sub>ClN<sub>2</sub>O<sub>5</sub>

Molecular weight: 505.05

Appearance: White or almost white powder.

Solubility: Freely soluble in water and solutions of physiological pH (1.0, 4.5 and 6.8). It is freely soluble in methanol and slightly soluble in acetone.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture, control, packaging and stability of the active substance.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

### **II.3. Medicinal Product Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing 5 mg or 7.5 mg, ivabradine (as hydrochloride) per tablet, that are generic versions of the reference products Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film-coating medium which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of anhydrous lactose, none of the excipients used contain material of animal or human origin. The supplier of anhydrous lactose has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

#### **Manufacture of the products**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and has shown satisfactory results.

#### **Finished Product Specification**

The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

#### **Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 36 months for the unopened blisters with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

There are no objections to the approval of these applications from a pharmaceutical viewpoint.



### III NON-CLINICAL ASPECTS

#### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ivabradine hydrochloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

#### III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Ivabradine 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.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical viewpoint.

### IV CLINICAL ASPECTS

#### IV.1 Introduction

The clinical pharmacology of ivabradine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of ivabradine hydrochloride.

Based on the data provided, Ivabradine can be considered bioequivalent Procoralan 5mg and 7.5mg film-coated tablets (Les Laboratoires Servier).

#### IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence study:

#### STUDY

An open-label, randomised, two-treatment, two-sequence, two-period, two-way crossover, single-dose, bioequivalence study of the applicant's test product Ivabradine 7.5 mg film-coated tablets (Mercury Pharmaceuticals Limited) versus the reference product Procoralan 7.5mg film-coated tablets (Les Laboratoires Servier) in healthy, adult, subjects under fed conditions.

Subjects were administered a single oral dose (1 x 7.5 mg tablet) of the test or reference product at about 30 minutes after being served a standardised high-fat and high-calorie breakfast.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

**Table: Summary of pharmacokinetic data for ivabradine (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  median, range):**

<b>Ivabradine</b>					
<b>Treatment</b>	<b>AUC<sub>0-t</sub></b> ng/ml/h	<b>AUC<sub>0-∞</sub></b> ng/ml/h	<b>C<sub>max</sub></b> ng/ml	<b>t<sub>max</sub></b> h	<b>T<sub>1/2</sub></b> h
<b>Test</b>	221.932 (±92.900)	232.834 (±95.863)	51.161 (±21.063)	1.667 (0.667, 5.000)	3.039 (±1.528)
<b>Reference</b>	220.730 (±100.301)	229.882 (±102.809)	51.724 (±20.356)	2.000 (1.000, 3.500)	2.871 (±1.088)
<b>*Ratio (90% CI)</b>	101.43 (97.68-105.32)	102.15 (98.28 -106.16%)	97.63 (92.26-103.30)		
<b>CV (%)</b>	9.607	9.832	14.448		
<b>AUC<sub>0-t</sub></b>	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC <sub>0-72h</sub> can be reported instead of AUC <sub>0-t</sub> , in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products				
<b>AUC<sub>0-∞</sub></b>	Area under the plasma concentration curve extrapolated to infinite time. AUC <sub>0-∞</sub> does not need to be reported when AUC <sub>0-72h</sub> is reported instead of AUC <sub>0-t</sub>				
<b>C<sub>max</sub></b>	Maximum plasma concentration				
<b>t<sub>max</sub></b>	Time until C <sub>max</sub> is reached				

\*ln-transformed values

**Study conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for ivabradine lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr\*\*). Thus, the data support the claim that the applicant's test product Ivabradine 7.5 mg film-coated tablets (Mercury Pharmaceuticals Limited) is bioequivalent to the reference product Procoralan 7.5mg film-coated tablets (Les Laboratoires Servier).

As the 5 mg and 7.5 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 7.5 mg tablet strength can be extrapolated to the 5 mg strength tablets.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for applications of this type.

**IV.4 Clinical efficacy**

No new efficacy data were submitted and none were required for applications of this type.

**IV.5 Clinical safety**

No new safety data were submitted and none are required.

**IV.6 Risk Management Plan (RMP) and Pharmacovigilance System**

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<b>Summary of safety concerns</b>	
Important identified risks	<ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• Phosphenes/ blurred vision</li> <li>• 2nd and 3rd degree atrioventricular blocks (AVB II and III)</li> <li>• Increase in blood pressure in hypertensive patients</li> <li>• Atrial fibrillation</li> <li>• Prolonged QT interval on ECG</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Supra-ventricular tachyarrhythmia other than atrial fibrillation</li> <li>• Immune disorders</li> <li>• Severe ventricular arrhythmia</li> <li>• Myocardial infarction</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Limited information on use in children under 18 years old</li> <li>• Limited information on use in pregnancy and breastfeeding women</li> <li>• Severe hepatic insufficiency</li> <li>• Severe renal impairment</li> <li>• Limited information on use in chronic heart failure patients with intra-ventricular conduction defects</li> </ul>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

#### **IV.7 Discussion on the clinical aspects**

The grant of marketing authorisations is recommended for these applications from a clinical viewpoint.

#### **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 language used for the purpose of user testing the PIL was English.

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**

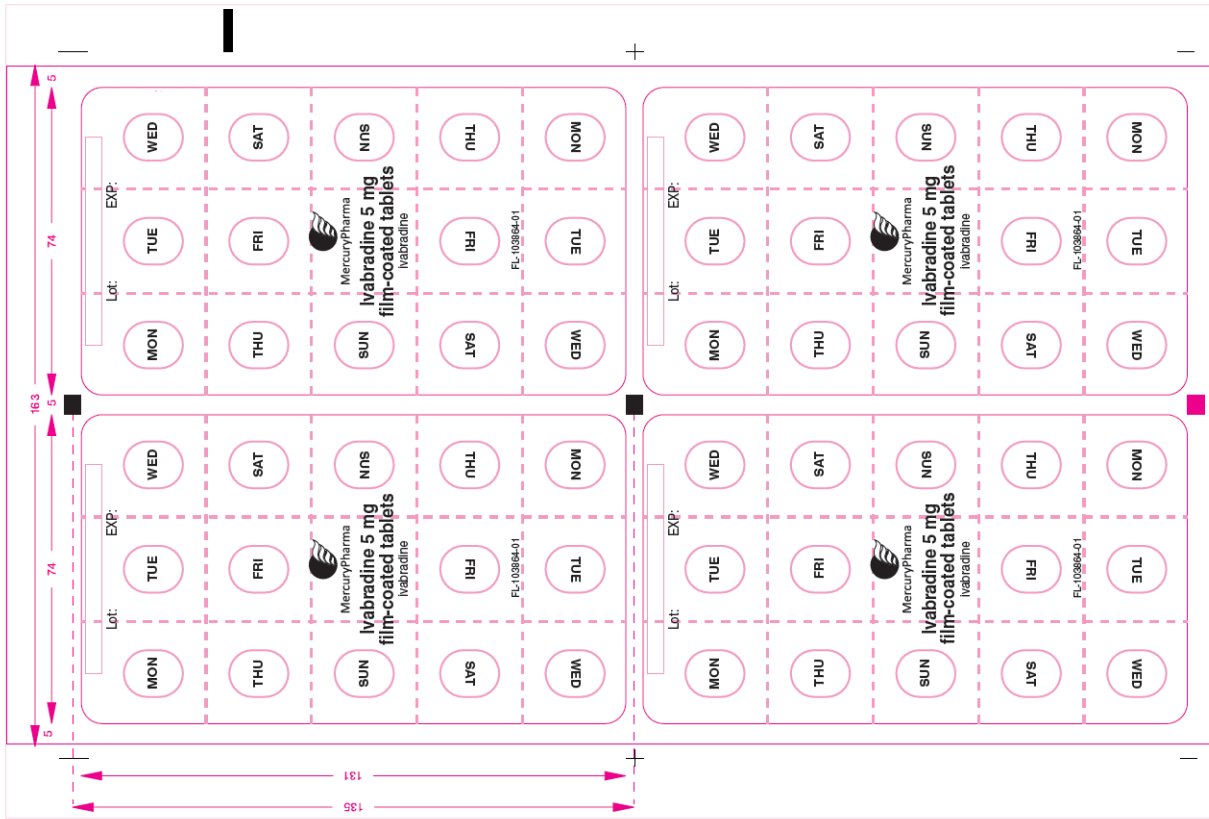
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ivabradine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The products are bioequivalent to the marketed reference products and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.

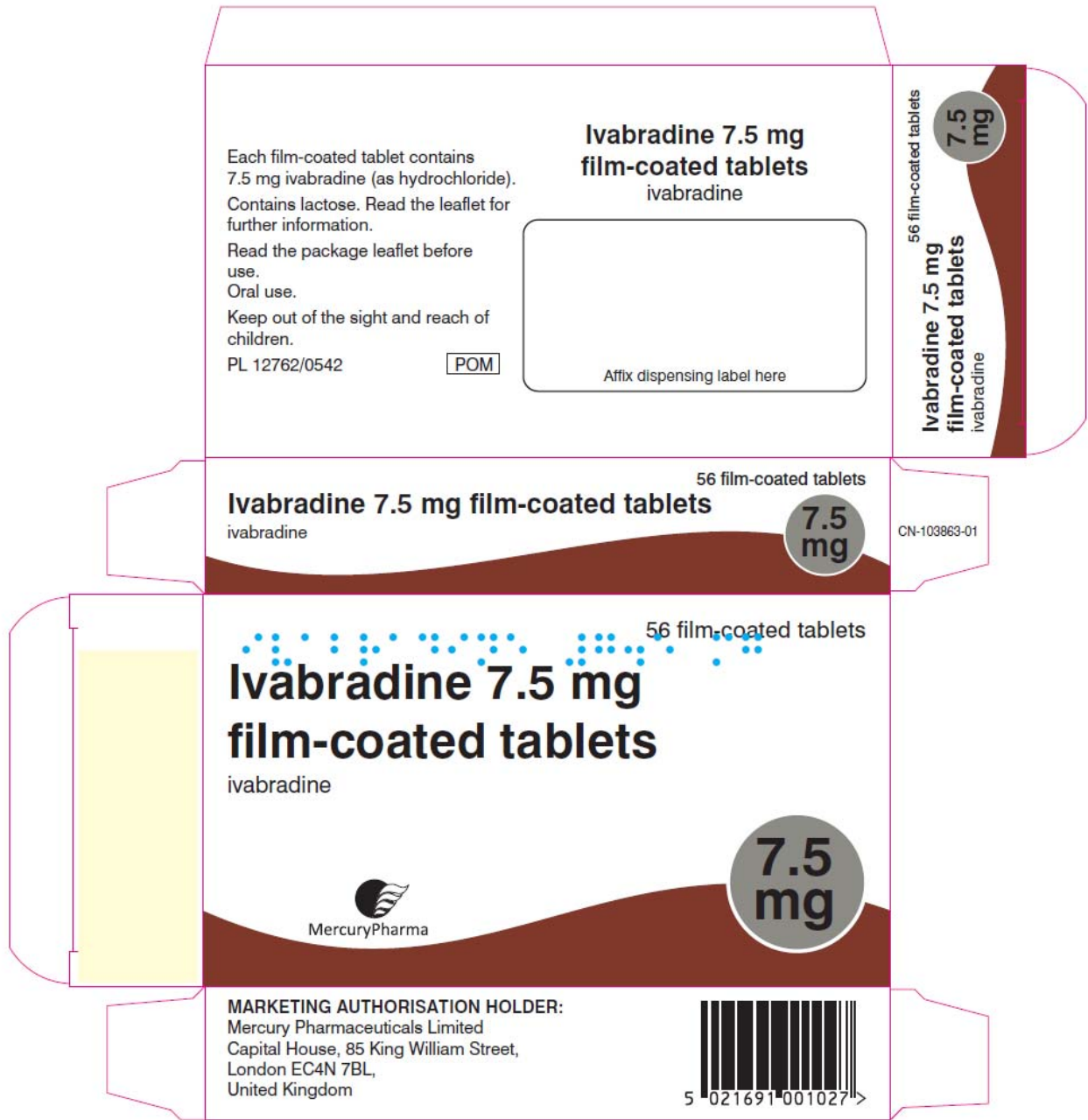
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

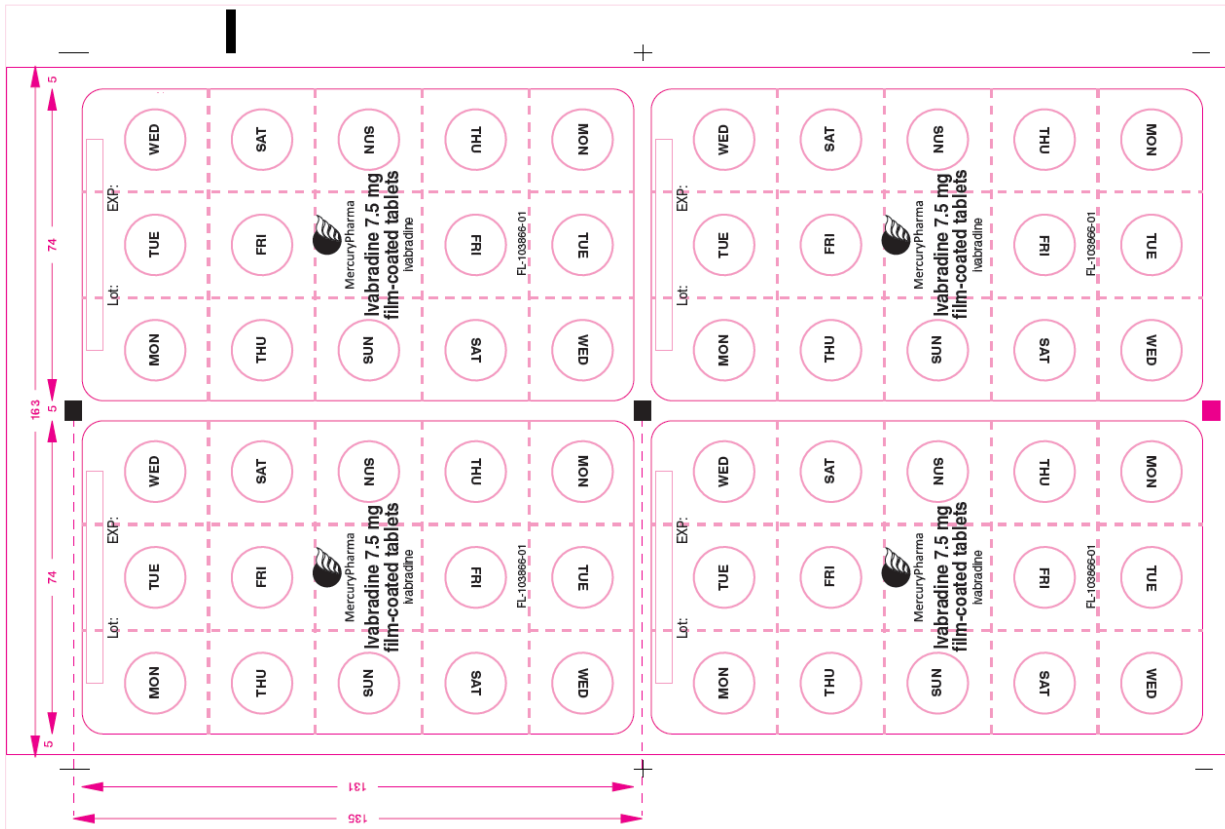
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:









## Annex 1

### Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome