EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/CHMP/594878/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivabradine Anpharm

International non-proprietary name: Ivabradine

Procedure No. EMEA/H/C/004187/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Background information on the procedure

1.1. Submission of the dossier

The applicant ANPHARM Przedsiębiorstwo Farmaceutyczne S.A. submitted on 5 May 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ivabradine Anpharm, through the centralised procedure under Article 3 (2) (a). The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2015.

The applicant applied for the following indication:

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.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information with a letter from Les Laboratoires Servier allowing the cross reference to relevant quality, non-clinical and/or clinical data.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The cross reference product Procoralan was given a Community Marketing Authorisation on 25 October 2005.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 5 May 2015.
- The procedure started on 25 May 2015.
- The Rapporteurs first Assessment Report was circulated to all CHMP members on 30 June 2015.
- During the meeting on 23 July 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ivabradine Anpharm.

2. Scientific discussion

2.1. Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended. The MAH of the reference product, Procoralan, has provided consent to allow access to Modules 2 to 5 of the initial dossier and any subsequent post-marketing procedures submitted, assessed and approved. Procoralan had been submitted as a full application under Art 8(3) of Directive 2001/83/EC. As a consequence, quality, safety and efficacy of Ivabradine Anpharm are identical to the up to date quality, safety and efficacy profile of Procoralan.

Procoralan is indicated in:

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.

The active substance of Ivabradine Anpharm is ivabradine hydrochloride, a heart rate (HR) lowering agent with specific effect on the sinus node with no effects on intra-atrial, atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarisation.

Ivabradine selectively blocks the f-channel in the pacemaker cells of the sinus node by entering and binding to a site in the channel pore. By inhibiting ion flow through the f-channel, ivabradine reduces the f-current (If) thus reducing the slope of the slow diastolic depolarisation phase of the action potential in the sinus node cells, thereby increasing the time required to reach the voltage threshold for action potential initiation. This in turn slows the spontaneous firing of sino-atrial node cells and therefore the heart rate (HR). Electrophysiological studies in sino-atrial node cells have demonstrated that, at therapeutic doses, ivabradine does not act on any other cardiac ion currents (IK, ICaL or ICaT). Ivabradine exerts a pure heart rate lowering effect without any direct effect on myocardial contractility and relaxation, cardiac output, coronary haemodynamics, blood pressure and peripheral resistance.

The application for Ivabradine Anpharm consists only of Module 1 information.

Compliance with GLP, GMP, GCP

No new preclinical studies were conducted, which is acceptable given that this is an informed consent application. The product has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as Procoralan.

No clinical studies were conducted, which is acceptable given that this is an informed consent application. The clinical studies conducted for the original Procoralan applications were considered to be in accordance with the appropriate GCP guidelines for the ethical treatment of human subjects.

The CHMP has been assured that acceptable standards of GMP are in place for this product. The proposed sites of manufacture are the same as currently approved for Procoralan. For manufacturing sites within the community, the CHMP has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

2.2. Quality aspects

Since this application is an informed consent of the Procoralan, the quality data in support of the Ivabradine Anpharm application are identical to the up-to-date quality data of the Procoralan dossier, which has been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

2.3.1. Introduction

Reference has been made to Module 4 data for Procoralan, no additional studies have been provided. Since this application is an informed consent of the Procoralan application, the non-clinical data in support of the Ivabradine Anpharm application are identical to the up-to-date non-clinical data of the Procoralan dossier, which have been assessed and approved, including all post-marketing procedures.

2.3.2. Ecotoxicity/environmental risk assessment

In accordance with the scope described in the CHMP guideline, given that this application is for products that are already authorized, the absence of a phased approach ERA as specified in the guideline, is considered justified in that the total quantity of the drug substance ivabradine hydrochloride is not expected to increase upon

approval of this marketing authorization. The applicant has referred to the Environmental Risk Assessment for Procoralan. Marketing of Ivabradine Anpharm in Europe is not expected to increase the environmental risk.

2.3.3. Conclusion on the non-clinical aspects

In this informed consent application, there are no new issues related to the non-clinical data. All the non-clinical data have been assessed for Procoralan application and adequately reflected in the Product Information.

2.4. Clinical aspects

2.4.1. Introduction

Reference has been made to Module 5 data for Procoralan, no additional studies have been provided. Since this application is an informed consent of the Procoralan application, the clinical data in support of the Ivabradine Anpharm application are identical to the up-to-date clinical data of the Procoralan dossier, which have been assessed and approved, including all post-marketing procedures.

2.4.2. Conclusions on the clinical aspects.

In this informed consent application, there are no new issues related to the clinical data. All the clinical data have been assessed for Procoralan application and adequately reflected in the Product Information.

2.5. Risk Management Plan

The risk management plan (RMP), version 5.1, has been provided for Procoralan/Corlentor. This RMP has been updated only to include Ivabradine Anpharm as it will also apply to Ivabradine Anpharm. Version 5.0 of the RMP for Procoralan has previously been assessed and was considered acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfil the requirements of Article 8(3) of Directive 2001/83/EC.

2.7. Product information

Product Information

The proposed SmPC and PL are the same as the currently approved SmPC and PL for Procoralan but one additional correction was requested to the SmPC section 6.6. In order to protect the environment the applicant was asked to add the following standard disposal advice to section 6.6 of the SmPC: “Any unused medicinal product or waste material should be disposed of in accordance with local requirements.”

Consultation with target patient groups

Consultation with target patient groups has not been undertaken for Ivabradine Anpharm. The content of the package leaflet is identical to the latest approved leaflet of Procoralan and therefore no further testing is warranted.

Braille

The product name and strength will be included on the outer cartons in Braille. The format will be in accordance with the recommendations of the European Commission.

3. Benefit-Risk Balance

This Marketing Authorisation application for Ivabradine Anpharm has been submitted by ANPHARM Przedsiębiorstwo Farmaceutyczne S.A. as an informed consent application in accordance with Article 10c of Directive 2011/83/EC, as amended.

As a consequence, quality, safety and efficacy of the Ivabradine Anpharm medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Procoralan. The application for Ivabradine Anpharm concerns the identical strengths to those approved for Procoralan and consists of only Module 1. Information on the scientific discussion can be found on the Procoralan CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

Consequentially, and in line with the assessment of data undertaken in the framework of the Procoralan initial marketing authorisation application as well as within all post-autorisation procedures, the CHMP considers that the benefit/risk balance for Ivabradine Anpharm is positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ivabradine Anpharm in the

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is favourable and therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
A drug utilisation study conducted in several EEA countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine, and adherence to the risk minimisation measures.	June 2018