LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Amiodaron Evolan
# (amiodarone hydrochloride)

# Asp no: 2021-0033, 2021-0034

**This module reflects the scientific discussion for the approval of Amiodaron Evolan. The procedure was finalised on 2022-01-31. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Amiodaron Evolan, 100 mg and 200 mg, Tablet.

The active substance is amiodarone, amiodarone hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Amiodaron Evolan, 100 mg and 200 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC.. The applicant, Evolan Pharma AB, applies through the Swedish National Procedure.

*For 100 mg*
The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cordarone, 100 mg, tablet authorised in Sweden since 1989, with Sanofi AB as marketing authorisation holder.

*For 200 mg*
The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cordarone, 200 mg, tablet authorised in Sweden since 1987, with Sanofi AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Cordarone, 200 mg, tablet from PT with Sanofi-Produtos Farmaceuticos. LDA as marketing authorisation holder.

**Potential similarity with orphan medicinal products**
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of amiodarone hydrochloride are well known. As amiodarone hydrochloride is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

**Environmental Risk Assessment (ERA)**
Since Amiodaron Evolan is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Amiodarone with the reference product Cordarone.

Pharmacokinetic properties of the active substance
*Absorption:* The oral bioavailability of amiodarone varies between 30 and 80% (mean value approximately 50%). After single-dose administration the maximum plasma concentration occur after 3 to 7 hours.

*Elimination:* The elimination is varying and slow with a reported half-life from 20 to 100 days after long-term treatment.

Study C1B00014
*Methods*
This was a single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Amiodarone, 200 mg, tablet with Cordarone, 200 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of amiodarone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-t}$ and $C_{max}$. The clinical part of the study was conducted between 24 Jul 20 and 08 Sept 20.

*Results*
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for amiodarone, n=37.**

| Treatment | $AUC_{0-72h}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **4806.151 ± 1872.946** | **258.084 ± 107.909** | **7.000 (5.000 -10.000)** |
| **Reference** | **4997.667 ± 1760.257** | **274.194 ± 100.628** | **7.500 (6.000 -10.000)** |
| ***Ratio (90% CI)** | **94.77 (88.07-101.98)** | **92.74 (84.23-102.11)** | **-** |
| $AUC_{0-t}$ 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 plasma concentration | | | |

**calculated based on ln-transformed data*

For $AUC_{0-72}$ and $C_{max}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 100 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The bioanalytical method was adequately validated.

Based on pharmacological and pharmacokinetic considerations it is concluded that amiodarone is not considered to be a narrow therapeutic index (NTI) drug. Even though there is large inter-individual variability in amiodarone pharmacokinetics, a maintenance dose of 200 mg is suitable in most patients and only two dose strengths (100 mg and 200 mg) are available for potential dose adjustments. Hence, the normal acceptance criteria 80.00-125.00% can be applied and narrowing of the acceptance limits to 90.00-111.11% is not needed.

Absence of studies with the additional strength of 100 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and since there are no indication of non-linear pharmacokinetics (less than proportional than dose) over the therapeutic dose range.

Based on the submitted bioequivalence study, Amiodaron Evolan is considered bioequivalent with Cordarone.

**Pharmacodynamics/Clinical efficacy/Clinical safety**

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

**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 Amiodaron Evolan.

Safety specification

The MAH has submitted the version 0.2 RMP dated 21st of July 2021 where they updated the proposed the following summary safety concerns into:

| SUMMARY OF SAFETY CONCERNS | |
|---|---|
| Important identified risks | -None |
| Important potential risks | -None |
| Missing information | -None |

**Assessor's comment:** The applicant has suggested safety concerns that are in line with other recently approved amiodarone containing products. This is considered acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 2021-07-21 is considered acceptable.

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 MPA;
- 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, but via different procedures.

# 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 PlL 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 generic product, Amiodaron Evolan, is found adequate. There are no objections to approval of Amiodaron Evolan, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive and the application is therefore recommended for approval.

**List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

Amiodaron Evolan, 100 mg, 200 mg, Tablet was approved in the national procedure on 2022-01-31.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se