COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Flecainide Alkaloid-INT 50 mg and 100 mg tablets (flecainide acetate)

NL/H/4923/001-002/DC

Date: 12 August 2021

This module reflects the scientific discussion for the approval of Flecainide Alkaloid-INT 50 mg and 100 mg tablets. The procedure was finalised at 23 March 2021. 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 Flecainide Alkaloid-INT 50 mg and 100 mg tablets, from Alkaloid-INT d.o.o..

The product is indicated for:

- AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways, when other treatment has been ineffective.
- Severe symptomatic and life-threatening paroxysmal ventricular arrhythmia which has failed to respond to other forms of therapy or where other treatments have not been tolerated.
- Paroxysmal atrial arrhythmias (atrial fibrillation, flutter and tachycardia) in patients with disabling symptoms after conversion provided that there is definite need for treatment on the basis of severity of clinical symptoms, when other treatment has been ineffective.

Structural heart disease and/or impaired left ventricular function should be excluded because of the increased risk for pro-arrhythmic effects.
Flecainide acetate tablets can be used for the maintenance of normal rhythm following conversion by other means.

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 Tambocor 50 mg and 100 mg tablets (RVG 15854 and RVG 10098) which have been registered in The Netherlands by Mylan Healthcare B.V. since 1993 and 1984 respectively, both through a national procedure.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Germany, Poland and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Flecainide Alkaloid-INT 50 mg is a white to off-white, round, biconvex tablet. Each immediate-release tablet contains 50 mg flecainide acetate.

Flecainide Alkaloid-INT 100 mg is a white to off-white, round, biconvex tablet with a score line on one side. The tablet can be divided into equal doses. Each immediate-release tablet contains 100 mg flecainide acetate.

The tablets are packed in PVC/PVDC/Aluminium foil blisters.

The excipients are pregelatinised starch (partially pregelatinised maize starch), croscarmellose sodium, microcrystalline cellulose, hydrogenated vegetable oil and magnesium stearate.

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is flecainide acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, very hygroscopic, crystalline powder. The powder is soluble in water and in anhydrous ethanol, freely soluble in dilute acetic acid and practically insoluble in dilute hydrochloric acid.
Flecainide acetate displays polymorphism. The drug substance manufacturing process results in polymorphic form I at both manufacturing sites, confirmed by differential scanning calorimetry (DSC) analysis performed by the drug product manufacturer. The polymorphic form I remains stable during the manufacturing process of the drug product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is in-line with the CEPs, with additional requirements for particle size distribution. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches of each CEP holder.

Stability of drug substance
The active substance from one manufacturer is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The active substance from the other manufacturer is stable for four years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batch used in the bioequivalence study is identical to the marketed product. Comparative dissolution profiles at three pHs have been provided. Breakability studies in accordance with the current Ph. Eur. are provided for the 100 mg strength.

Manufacturing process

The tablets are manufactured by wet granulation. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scaled batches of each strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph. Eur. requirements where applicable, or with other relevant compendial requirements. 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, dissolution, assay, related substances, uniformity of dosage units and microbial quality. The absence of a test for water content is justified. Limits for impurities are acceptable. The limit for dissolution has been set in line with the dissolution of the batch used in the bioequivalence study. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches, as well as one pilot scale batch per strength stored at 25°C/60% RH (18 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended blisters. The drug product is generally very stable in the proposed container packaging system and no general trends or signs of degradation are observable. Total impurities are below reporting threshold for all batches at all time-points under all storage conditions. No change in dissolution and assay is noticed for the time-frame covered so far. Hence, extrapolation by 6 months up to the requested shelf-life of 24 months is considered acceptable. Photostability

data in accordance with ICH show that the product is stable when exposed to light. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning 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 Flecainide Alkaloid-INT 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 Flecainide Alkaloid-INT 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 Tambocor 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

Flecainide acetate 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. A biowaiver is applied for the lower strength of 50 mg tablets.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Flecainide Alkaloid-INT 100 mg tablets (Alkaloid - INT d.o.o., Slovenia) is compared with the pharmacokinetic profile of the reference product Tambocor 100, 100 mg tablets (Mylan Healthcare B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition of the Dutch reference product.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver was requested for the 50 mg strength. All requirements as stated in the Bioequivalence Guideline with respect to manufacturing process, qualitative and quantitative composition, and linearity of pharmacokinetics appear to be met. Comparative dissolution data were provided in support of the requested biowaiver for the additional 50 mg strength. Comparative dissolution at the required conditions between the 50 mg and 100 mg strength is considered sufficiently demonstrated at pH 1.2, 4.5 and 6.8. Therefore, the biowaiver has been granted.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions. in 28 healthy male and female subjects, aged 19-55 years. Each subject received a single dose (100 mg) of one of the two flecainide acetate formulations. The tablet was orally administered with water after a supervised overnight fast. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected prior to and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 9, 12, 24, 36, 48 and 72 hours after administration of the product.

The design of the study is acceptable. Flecainide acetate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of flecainide acetate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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 male subjects discontinued the study. One subject was discontinued prior to dosing of period 2, due to adverse events (hypertension and chest pain). The other subject withdrew consent after dosing of period 1 for personal reasons. 26 Subjects were eligible for pharmacokinetic analysis.

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

Treatment N=26	AUC_{0-72} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)	t_{max} (h)
Test	2219.2 ±796.4	2313.6 ± 833.0	150.4 ± 47.3	1.33 (1.00 – 3.67)
Reference	2174.2 ±746.0	2284.3 ±785.8	138.6 ± 40.0	1.67 (1.00 – 3.00)
***Ratio (90% CI)**	1.02 (0.97 – 1.06)	-	1.08 (1.03 – 1.14)	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-72}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Flecainide Alkaloid-INT is considered bioequivalent with Tambocor.

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 *Flecainide Alkaloid-INT*.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Proarrhythmic effects • Cardiac conduction disorders • Adverse hemodynamic effects, including cardiac failure • Worsening of hepatic function
Important potential risks	• Interaction with CYP2D6 inducer/inhibitor • Hypokalaemia on concomitant use with diuretics, corticosteroids or laxatives
Missing information	• Use in the paediatric population under 12 years old • Use during pregnancy and lactation

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 Tambocor. 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 (PL) 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 PL was English. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Flecainide Alkaloid-INT 50 mg and 100 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Tambocor 50, 50 mg tablets and Tambocor 100, 100 mg

tablets respectively. Both strengths of Tambocor are well-known medicinal products 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 Flecainide Alkaloid-INT with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 March 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4923 /IB/001/G	Type IA: B.II.e.5.a.1; Type IB: B.II.e.5.a.2– To introduce a new pack size of 50 tablets	Yes; PL, SmPC and Label	21-05-2021	Approval	