CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Flecaïnideacetaat 50 mg, tablets
Flecaïnideacetaat 100 mg, tablets
Hexal AG, Germany

flecainide acetate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0795/001-002/MR
Registration number in the Netherlands: RVG 31787, 31788

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Pharmacotherapeutic group:	Antiarrhythmics, class Ic
ATC code:	C01BC04
Route of administration:	oral
Therapeutic indication:	treatment of AV nodal reciprocating tachycardia; severe symptomatic and life-threatening paroxysmal ventricular arrhythmia; paroxysmal atrial arrhythmias.
Prescription status:	prescription only
Date of authorisation in NL:	20 October 2004
Concerned Member States:	BE, DE, DK, LU, SK; 100 mg only - FI, IT, NO, SE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Flecaïnideacetaat 50 mg, tablets and Flecaïnideacetaat 100 mg, tablets from Hexal AG, Germany. The date of authorisation was on 20 October 2004 in the Netherlands.

The product is indicated for the treatment:

- 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. Also where other treatments have not been tolerated.
- Paroxysmal atrial arrhythmias (atrial fibrillation, atrial flutter and atrial 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.

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

Electrophysiologically, flecainide is a local anaesthetic-type (Class IC) of antiarrhythmic compound. It is an amide type of local anaesthetic, being structurally related to procainamide and encainide in so far as these agents are also benzamide derivatives.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Tambocor 50, tablets 50 mg and Tambocor 100, tablets 100 mg (NL License RVG 15854 and 10098). The innovator products have been registered in the Netherlands by Meda Pharma B.V. since 27 January 1993 and 25 January 1984, respectively. In addition, reference is made to Tambocor authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Flécaïne comprimé 100 mg tablet by Laboratoires 3M Santé, registered in France. Flécaïne comprimé is the French name for the innovator product Tambocor. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is flecainide acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance specification is adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with in-house specifications for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for 6 batches.

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.

Stability data supporting the retest period are submitted, as well as a stress test. No trends were observed. Based on these results, a retest period was granted of 2 years without special storage conditions.

The excipients used are well-known and common for tablets. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs, except for microcrystalline cellulose, for which an in-house method is submitted. The specifications of the excipients are acceptable.

**Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Flecaïnideacetaat 50 mg and Flecaïnideacetaat 100 mg contain 50.0 and 100.0 mg flecainide acetate, respectively.

The Flecaïnideacetaat 50 mg tablets are white, circular, biconvex, uncoated and embossed "C" on one face and the identifying letters "FI" on the reverse.
The Flecaïnideacetaat 100 mg tablets are white, circular, biconvex, uncoated and embossed with a breakline on one face with the identifying letters "C" above the line and "FJ" below, the reverse with a breakline. The tablets are supplied in PVC/PVDC/Al-blisters and containers of polypropylene with snap-on polyethylene lids.

The excipients are: croscarmellose sodium (E 468), magnesium stearate (E 470b), pregelitinized maize starch, maize starch and microcrystalline cellulose (E460).

Pharmaceutical development
The product is an established pharmaceutical form and its development has been described extensively in accordance with the relevant European guidelines. The packagings are usual and suitable for the product.

The aim was to develop a product with similar characteristics as the innovator Tambocor.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 2 full scale batches of 50 mg and 4 full scale batches of 100 mg strength in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications are based on the monograph for tablets in the Ph.Eur. and include tests for appearance, identification, average weight, uniformity of mass, disintegration, dissolution rate, hardness, thickness, diameter, friability, assay, related substances and microbiological purity. Limits in the specifications 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 for 4 production scaled batches of 50 mg and 3 production scaled batches of 100 mg have been provided, demonstrating compliance with the specifications.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches for each strength in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. Based on these data, a shelf life of 3 years was granted. No specific storage conditions need to be included in the SPC 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.2 Non clinical aspects

This product is a generic formulation of Tambocor, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of flecainide acetate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Flecainide acetate is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Tambocor.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Flecaïnideacetaat 100 mg, tablets is compared with the French reference product Flécaïne comprimé 100 mg tablets. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The SPC mentioned in order to avoid the possibility of food affecting the absorption of the drug, that flecainide should be taken on an empty stomach or one hour before food. Therefore, a food interaction study was not deemed necessary.

A randomised, open-label, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy volunteers (12 male and 12 female), aged 19-45 years. Each subject received after an overnight fast of at least 10 hours a single dose (100 mg) of one of the 2 flecainide acetate formulations. The tablets were administered with 200 ml of noncarbonated water. For each subject there were 2 dosing periods, separated by a washout period of 7 days. Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 16, 24, 36, and 48 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of flecainide under fasted conditions

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2317 ± 808	2623 ± 922	157 ± 37.3	2 (1-4.55‡)	12.1 ± 3.4
Reference	2342 ± 787	2666 ± 920	153 ± 39.0	1.5 (0.5–4.98‡)	12.6 ± 3.7
***Ratio (90% CI)**	1.01 (0.97-1.05)	1.02 (0.98-1.05)	0.97 (0.92-1.02)	--	--
CV (%)	16	7	12	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
*	ln-transformed values
‡	blood samples respectively taken 5 minutes after and 2 minutes before scheduled time

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of flecainide under fasted conditions, it can be concluded that test Flecaïnideacetaat 100 mg tablets and the French reference Flécaïne comprimé 100 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 50 mg tablets are dose proportional with the 100 mg tablets. The *in vitro* dissolution profiles show rapid dissolution for all tablets tested (>80% within 30 minutes). Therefore, the results of the bioequivalence study performed with the 100 mg strength apply to the 50 mg strength.

The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

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).

Risk Management Plan

Flecainide was first approved in 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of flecainide can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post-authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is

based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed Risk Management Plan is not necessary for this product.

Readability test

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 test consisted of two rounds, with 10 participants each. After the first test the MAH revised the leaflet in several sections and a second test with 10 participants was performed. This led to an increase in the number of respondents who gave a correct answer (now 76%) and a decrease in the number of those who gave an incorrect answer (now 11%). Although the target of 80% correctly answered questions has not been achieved, it can be concluded that the readability of the leaflet is of an acceptable level. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been acceptably performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Flecaïnideacetaat 50 mg, tablets and Flecaïnideacetaat 100 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Tambocor. Tambocor 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 content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Tambocor.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Flecaïnideacetaat 50 mg and Flecaïnideacetaat 100 mg with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between the member states was reached during a written procedure.

The first PSUR cycle will cover a 3 year period from 1 August 2006 until 1 August 2009. The second PSUR will cover a 2 year period to coincide with the renewal. Hereafter, the PSURs will be submitted three-yearly.

The date for the first renewal will be 1 August 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a new manufacturer (replacement or addition). Other substances.	NL/H/0795 /001-002/ IA/001	IA	28/11/2007	12/12/2007	Approval	N
Update of open part DMF.	NL/H/0795 /001-002/ II/002	II	4/2/2009	5/4/2009	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/0795 /001-002/ IA/003	IA	19/1/2009	2/2/2009	Approval	N
Change in the wording of the warning concerning initiation of therapy with Flecainide in section section 4.2 and 4.4 in the SPC and corresponding sections in the Package Leaflet.	NL/H/0795 /001-002/ II/004	II	22/7/2009	13/12/2009	Approval	N