CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Flecaïnideacetaat Aurobindo 50 mg and 100 mg, tablets
Aurobindo Pharma B.V., the Netherlands

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/2428/001-002/DC
Registration number in the Netherlands: RVG 110550 - 110551

13 December 2012

Pharmacotherapeutic group:	antiarrhythmics, class IC
ATC code:	C01BC04
Route of administration:	oral
Therapeutic indication:	AV nodal reciprocating tachycardia; severe symptomatic and life-threatening paroxysmal ventricular arrhythmia; paroxysmal atrial arrhythmias
Prescription status:	prescription only
Date of first authorisation in NL:	10 October 2012
Concerned Member States:	Decentralised procedure with DE, ES (only 100 mg), IT (only 100 mg), MT and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) and 10(3)

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 member states have granted a marketing authorisation for Flecaïnideacetaat Aurobindo 50 mg and 100 mg, tablets, from Aurobindo Pharma B.V. The date of authorisation was on 10 October 2012 in the Netherlands.

The product is indicated for:

- Treatment of AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways, when other treatment has been ineffective.
- Treatment of 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.
- Treatment of 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.

Flecainide acetate is a Class IC antiarrhythmic agent used for the treatment of severe symptomatic life-threatening ventricular arrhythmias and supraventricular arrhythmias.
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.
The characterisation of flecainide as a Class IC compound is based on a triad of features: marked depression of the fast sodium channel in the heart; slow onset and offset kinetics of inhibition of the sodium channel (reflecting slow attachment to and dissociation from sodium channels); and the differential effect of the drug on the action potential duration in ventricular muscle versus Purkinje fibres, having no effect in the former and markedly shortening it in the latter. This composite of properties leads to a marked depression in conduction velocity in fibres dependant on the fast-channel fibres for depolarisation but with a modest increase in the effective refractory period when tested in isolated cardiac tissues. These electrophysiological properties of flecainide acetate may lead to prolongation of the PR-interval and QRS duration on the ECG. At very high concentrations flecainide exerts a weak depressant effect on the slow channel in the myocardium. This is accompanied by a negative inotropic effect.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tambocor 100 mg tablets (NL License RVG 10098) which has been registered in the Netherlands by Meda Pharma B.V. since 25 January 1984 (original product). Tambocor 50 mg (NL License RVG 15854) was authorised on 27 January 1993. In addition, reference is made to Tambocor authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) and 10(3) (for the 50 mg tablet in Malta) 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 MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Tambocor 100 mg tablets, registered in the United Kingdom. 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. This generic product can be used instead of its 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 these products and no paediatric development programme has been submitted, as this is not required for a generic application.

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 this product type 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
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, which is soluble in water and in anhydrous ethanol. It is freely soluble in dilute acetic acid and practically insoluble in dilute hydrochloric acid. Flecainide acetate contains one chiral centre. The drug substance is a racemic mixture of the R and S enantiomer. No polymorphism has been reported.

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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is in line with the CEP, with additional requirements for content of acetate, particle size distribution, bulk density, polymorphic form and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for five full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scale batches stored at 25°C/60% RH (60 months) and at 40°C/75% RH (6 months). At both conditions an increase in loss on drying was observed. All results remained within specification limits.
Based on the stability data provided the proposed re-test period of 60 months and the proposed storage condition ‘Keep inner and outer bags tightly closed in order to protect from moisture and light’ can be granted.

** 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 Aurobindo 50 mg tablets are white to off-white, round [diameter 6.5 mm], biconvex tablets embossed with ‘CC’ on one side and ‘11’ on the other side.
Flecaïnideacetaat Aurobindo 100 mg tablets are white to off-white, round [diameter 8.5 mm], biconvex, scored tablets debossed with ‘1’ and ‘2’ separated by deep score line on one side and ‘CC’ on the other side. The tablet can be divided into equal halves

The tablets are packed in clear PVC/PVdC-Aluminium foil blister packs and HDPE bottle packs with polypropylene closure.

The excipients are: microcrystalline cellulose (E460), croscarmellose sodium, pregelatinized starch, hydrogenated vegetable oil, magnesium stearate (E572).

The different tablet strengths are fully dose proportional.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were formulation trials. Formulation trials were performed to investigate the effect of various extra granular excipients on flow properties, sticking and capping during compression and dissolution rate. The choice of manufacturing process and packaging has been adequately justified. Breakability data has been provided of three batches of 100 mg tablets, demonstrating compliance the Ph.Eur. requirements for subdivision. The dissolution profiles of the 50 mg and 100 mg strengths may be accepted as similar, as more than 85% is dissolved in 15 min at three pHs.
The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The bioequivalence batch is of sufficient size in relation to the intended commercial batch size. The bioequivalence study was performed against the UK reference product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is divided into the following steps: wet granulation, blending, lubrication and compression. The product is manufactured using conventional manufacturing techniques. Adequate process validation data of three batches of the smallest production scale of each strength has been provided. Process validation for batches of the maximum production scale will be performed post authorisation.

Control of excipients

The excipients comply with relevant Ph.Eur. monographs, except for hydrogenated vegetable oil which complies with the British Pharmacopoeia monograph. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, average mass, thickness, water content, related substances, assay, dissolution, mass variation, microbial contamination and subdivision of tablets (100 mg tablets). The release and shelf life limits are identical except for loss on drying. Given the observed increase in loss on drying during stability studies this is acceptable. The drug product specification is considered acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided three full-scale batches of each strength stored at 25°C/60% RH (12 months) and at 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 PVC-PVdC/Al blisters and HDPE containers (two sizes). The water content decreased in the larger container and remained relatively stable in the small container. However, the water content increased in the blister at both conditions. All results remained within specification limits.
All other parameters examined remained relatively stable throughout the test periods for all strengths at both conditions and within specification. Photostability studies have been performed on one batch of each strength in accordance with NfG on the Photostability Testing of New active substances and Medicinal Products. Flecainide tablets were directly exposed. No changes were observed in description, assay and related substances.

Based on the provided stability data, a shelf life of 24 months without special storage conditions was granted. Stability data has been provided demonstrating that the product remains stable for 12 months following in first opening of the container when stored at long term conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Declarations on the TSE/BSE safety have been provided. No material of human or animal origin is used in the manufacture of flecainide tablets. Magnesium stearate is of vegetable origin. A theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Tambocor tablets, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other 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.
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 a bioequivalence study in which the pharmacokinetic profile of the test product Flecaïnideacetaat Aurobindo 100 mg, tablets (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Tambocor 100 mg tablets (Meda Pharmaceuticals Ltd, UK).

The choice of the reference product
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 formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 19-41 years. Each subject received a single dose (100 mg) of one of the 2 flecainide acetate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected drawn pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours after administration of the products.
This design is in general acceptable. The study has been performed according to GCP.

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
A total of 24 healthy male subjects were dosed in both dosing periods, all of them completed the clinical phase of the study. There were no adverse events reported during this study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of flecainide acetate 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	2230 ± 486	2310 ± 514	117 ± 28	2.5 (0.5-8.0)	14.7 ± 2.3
Reference	2181 ± 527	2257 ± 565	117 ± 39	3.25 (0.5-8.0)	14.6 ± 2.2
***Ratio (90% CI)**	1.02 (0.98-1.07)	1.03 (0.98-1.07)	1.02 (0.96-1.09)	-	-
CV (%)	8.3	8.4	13.3	-	-

$AUC_{0-\infty}$ 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*

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 acetate under fasted conditions, it can be concluded that Flecaïnideacetaat Aurobindo 100 mgand Tambocor 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.

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.

Biowaiver
A biowaiver for the Flecaïnideacetaat Aurobindo 50 mg, tablets has been justified based on the following conditions:

- the manufacturing process is the same for both strengths
- the qualitative composition is the same for both strengths
- the tablets are quantitatively proportional
- the two strengths have comparable dissolution profiles
- the plasma concentration is dose proportional in the therapeutic range.

Risk management plan
Flecainide acetate was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of flecainide acetate 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 MAH 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 European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in line with the CSP (agreed in December 2011) and with that accepted for other flecainide acetate containing products.

Readability test
The MAH did not perform a user test but submitted a bridging report instead. The proposed PL is bridged regarding content to the PIL of another flecainide acetate containing product. The wording of the PL has been brought in line with the PIL of NL/H/0795/MR, therefore the bridging report is acceptable.
Regarding design and layout the proposed PIL is bridged to the PIL of Mirtazapine Aurobindo (NL/H/1261/01-03/MR). This is acceptable for the following reasons:

- Both Parent and daughter PILs have same layout and design (same in-house style).
- The critical safety sections (Contraindications & warnings) in both Parent PIL and Daughter PIL are laid out in bullet points.
- The paperweight of both Parent PIL and Daughter PIL is the same (40-45g/m2).
- Both PILs have been prepared according to the current QRD-template.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Flecaïnideacetaat Aurobindo 50 mg and 100 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Tambocor 50 mg and 100 mg tablets. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other flecainide acetate containing products.

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 Flecaïnideacetaat Aurobindo 50 mg and 100 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 August 2012. Flecaïnideacetaat Aurobindo 50 mg and 100 mg, tablets were authorised in the Netherlands on 10 October 2012.

The date for the first renewal will be: 13 May 2016.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to validate the first three batches of common blend of the larger production scales according to the provided validation protocol.
- The MAH committed to validate the first three batches of each strength of the largest production scale according to the provided validation protocol.
- The MAH committed to continue the on going long-term stability studies as per provided study design (*i.e.* up to 60 months).
- The MAH committed to include the first three production scale batches of the maximum batch size of each strength in accelerated and long-term stability studies (when manufactured).
- The MAH committed to continue the on-going in-use study up to the proposed shelf-life as per the study design.

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
CSP	Core Safety Profile
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
PIL	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