CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sotalol HCl 40 PCH, tablets 40 mg
Pharmachemie B.V., the Netherlands

sotalol hydrochloride

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 33884

19 July 2010

Pharmacotherapeutic group:	Beta blocking agents, non-selective
ATC code:	C07AA07
Route of administration:	oral
Therapeutic indication:	ventricular tachycardia, supraventricular tachycardia
Prescription status:	prescription only
Date of authorisation in NL:	27 July 2007
Application type/legal basis:	Directive 2001/83/EEC, Article 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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Sotalol HCl 40 PCH, tablets 40 mg from Pharmachemie B.V. The date of authorisation was 27 July 2007.

The product is indicated for prophylaxis of:
- life-threatening ventricular tachycardias;
- documented symptomatic and disabling ventricular tachycardias in the absence of uncontrolled heart failure;
- documented supraventricular tachycardias in the absence of uncontrolled heart failure when the need for treatment is established. (e.g. maintenance of sinus rhythm after conversion of atrial fibrillation or atrial flutter.)

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

D,l-sotalol is a non-selective hydrophilic β-adrenergic receptor blocking agent, devoid of intrinsic sympathomimetic activity or membrane stabilizing activity.
Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol has no known effect on the upstroke velocity and therefore no effect on the depolarisation phase.
Sotalol uniformly prolongs the action potential duration in cardiac tissues by delaying the repolarisation phase. Its major effects are prolongation of the atrial, ventricular and accessory pathway effective refractory periods.
The Class II and III properties may be reflected on the surface electrocardiogram by a lengthening of the PR, QT and QTC (QT corrected for heart rate) intervals with no significant alteration in the QRS duration.
The d- and l-isomers of sotalol have similar Class III antiarrhythmic effects while the l-isomer is responsible for virtually all of the beta-blocking activity. Although significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are usually seen at daily doses of greater than 160 mg.
Its β-adrenergic blocking activity causes a reduction in heart rate (negative chronotropic effect) and a limited reduction in the force of contraction (negative inotropic effect). These cardiac changes reduce myocardial oxygen consumption and cardiac work. Like other β-blockers, sotalol inhibits renin release. The renin-suppressive effect of sotalol is significant both at rest and during exercise. Like other beta adrenergic blocking agents, sotalol produces a gradual but significant reduction in both systolic and diastolic blood pressures in hypertensive patients.

This national application for marketing authorisation concerns Sotalol HCl 40 PCH, tablets 40 mg. The application is made in accordance with article 10(3) of Directive 2001/83/EC, hybrid application. The reference product is Sotacor 80 mg tablets, registered in the Netherlands by Bristol-Meyers Squibb B.V. since 19 December 1973 in under NL License RVG 06741. The strength of the reference product differs from the product applied for (40 mg).

The marketing authorisation is granted based on article 10(3) 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 Sotalol HCl 80 PCH is compared with the pharmacokinetic profile of the reference product Sotalex 80 mg tablets, registered in France. A biowaiver was granted; a bioequivalence study with the 40 mg tablet is therefore not required. 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 hybrid 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 hybrid 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 sotalol hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*), it is a racemate, no evidence is found (in literature and with own experiments) of different polymorphic forms. The active substance is a white or almost white crystalline powder, which is freely soluble in water, soluble in alcohol and practically insoluble in methylene chloride.

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/EMEA 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.

Manufacturing process
The active substance is manufactured in a four-step synthesis. The process is described in sufficient detail. Acceptable specifications and test methods are provided for the starting material and reagents, solvents and other processing aids used in the manufacture of sotalol.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 4 production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 11 batches. The drug substance was stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). No trends are observed either under accelerated conditions or long term conditions.
Based on the data submitted, a retest period could be granted of 5 years. The drug product should be stored in the original package in order to protect from light.

** 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
Sotalol HCl 40 PCH contains as active substance 40 mg of sotalol hydrochloride, and is a white to off-white, oval tablet, debossed with 'Sot 40' on one side.

The tablets are packed in PVC/PVdC/aluminium blisters.

The excipients are: lactose, maize starch, povidone K30 (E1201), magnesium stearate (E470b).

Pharmaceutical development
The formula of the tablets is based on the identical formula of the Sotalol 80 mg PCH (RVG 28268), from the same MAH and manufacturer already registered in the Netherlands. Therefore, no compatibility studies with excipients are necessary and no new method of manufacture was developed. This is acceptable. The formula is dose proportional to Sotalol 80 mg, except for a very small amount of colorant (0.01%).
A dissolution profile comparison study was conducted on 40 and 80 mg PCH tablets and Sotacor 80 mg. The three batches were comparable (>85% dissolved after 15 minutes). Therefore, the dissolution profiles can be accepted as similar according to the *NfG on the investigation of bioavailability and bioequivalence*.
The pharmaceutical development has been sufficiently elucidated.

Manufacturing process
The manufacturing process can be considered as a standard wet granulation process. The manufacture consists of blending, granulation and compression steps. Acceptable in-process controls have been laid down. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with their Ph.Eur. specifications. 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 appearance, identification, mean weight, uniformity of mass, disintegration, dissolution rate, thickness, resistance to crushing, friability, assay, related substances and microbiological purity. The analytical methods have been adequately described and validated.
Batch analytical data from 3 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the finished product have been provided for three batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The tablets were packed in PVC/PVdC/aluminium blisters. The results at accelerated and normal conditions did not show any trend and impurities could not be detected, so the product is very stable. In addition, the MAH submitted supporting data of the 80 and 160 mg strengths (24 months normal conditions; 6 months accelerated conditions). These two products are registered with a shelf-life of 3 years and no storage conditions. In view of the *NfG on stability testing for applications for variations to a marketing authorisation*, these results can be accepted. The stability studies will be continued. Based on the data provided, a shelf life of 2 years with no additional storage conditions could be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. TSE certificates have been provided for lactose and magnesium stearate. .

II.2 Non clinical aspects

This active substance has been available on the Dutch market since 1973. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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 sotalol 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

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

For this hybrid application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Sotalol HCl 80 PCH (Pharmachemie B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Sotalex 80 mg tablets (Bristol-Myers Squibb, France).

Design
A single-dose, randomised, balanced, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 18 healthy male subjects. Each subject received a single dose (80mg) of one of the 2 sotalol hydrochloride formulations. There were 2 dosing periods, separated by a washout period of 8 days.

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
All subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=18	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	10259	10904	852	3.0 (1.5-5.0)	-
Reference	9603	10402	781	3.0 (1.0-5.0)	-
***Ratio (90% CI)**	1.07 (1.00-1.14)	1.05 (1.00-1.11)	1.09 0.98-1.25)	-	-
CV (%)	-	-	-	-	-

$AUC_{0-\infty}$ 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 sotalol under fasted conditions, it can be concluded that Sotalol HCl 80 PCH and Sotalex 80 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.

Sotalol may be taken without reference to food intake. 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.

Extrapolation to 40 mg tablets
The 40 mg and 80 mg sotalol tablets are completely dose proportional. The dissolution profiles both strengths are similar under identical conditions. The tablets are manufactured by the same manufacturer and at the same manufacturing site. Sotalol pharmacokinetics are dose proportional in the appropriate dose range. Therefore the results of the bioequivalence study with the 80 mg tablet may be extended to the 40 mg tablets.

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
Sotalol was first approved in 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of sotalol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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 national procedure is in accordance with the product information accepted for other sotalole containing products.

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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sotalol HCl 40 PCH, tablets 40 mg has a proven chemical-pharmaceutical quality and is a hybrid form of Sotacor 80 mg tablets. Sotacor 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, package leaflet and labelling are in the agreed templates and are in agreement with other sotalole containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and have therefore granted a marketing authorisation. Sotalol HCl 40 PCH, tablets 40 mg was authorised in the Netherlands on 27 July 2007.

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
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
Change in the batch size of the finished product, upscaling up to 10-fold.	--	IA	27-9-2007	5-11-2007	Approval	N
Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass.	--	IA	27-9-2007	5-11-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product.	--	IA	25-5-2009	5-9-2009	Approval	N