CBG MEB

Public Assessment Report

Scientific discussion

Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection

(sotalol hydrochloride)

NL License RVG: 117148

Date: 5 December 2017

This module reflects the scientific discussion for the approval of Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection. The marketing authorisation was granted on 2 June 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection from TioFarma B.V.

The product is indicated for:

- treatment of acute ventricular arrhythmias, including life-threatening ventricular tachyarrhythmias, symptomatic non-sustained ventricular tachyarrhythmias.
- temporary substitution for oral therapy in patients who are unable to take oral sotalol.

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Sotacor, solution for injection 10 mg/ml (NL License RVG 10876) which was registered in the Netherlands by Bristol-Myers Squibb B.V. on 27 October 1986. This product was withdrawn for commercial reasons in 2012.

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

II. QUALITY ASPECTS

II.1 Introduction

Sotalol HCl Tiofarma is a clear, colourless solution. pH is between 4.0 and 6.0. Osmolality is approximately 310 mOsmol/L.
Each 4 ml type I glass ampoule contains 40 mg sotalol hydrochloride corresponding to 35.3 mg sotalol.

The excipients are: sodium chloride, acetic acid, sodium hydroxide (for pH adjustment), water for injections.

II.2 Drug Substance

The active substance is sotalol hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water. Particle size and polymorphic form of the active substance are not deemed critical since it will be used for a solution for injection.

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. 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 3 full scale batches.

Stability of drug substance
The active substance is stable for 5 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 choice of excipients is justified in view of the reference product and their functions have been explained. Sotalol HCl Tiofarma contains the same excipients as the innovator product. The pharmaceutical development of the product has been adequately performed. No overage or overfill is required. The choice of sterilisation method is justified. The filled one-point-cut ampoules are steam sterilized in an autoclave. Ph.Eur. recommendations regarding temperature and time are taken into account.

Manufacturing process
The manufacture of the drug product is straight-forward: preparation of the solution, sterile filtration, filling into ampoules, terminal sterilisation and packaging. The manufacturing process is considered a standard process. A validation protocol has been provided.

Control of excipients
The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for clarity, colour and odour of solution, pH, density, extractable volume, identity of active substance, assay, degradation products, sterility, bacterial endotoxins, particulate contamination and sub-visible particles. The release and shelf-life requirements are identical, except that the test for odour of the solution is not included in the shelf-life specification which is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on 3 full scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 3 pilot batches and 10 full scale batches stored at 25°C/60% RH (range 12 – 60 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 colourless glass type I glass ampoules (Ph.Eur.). No changes are observed at both storage conditions. Photostability of drug product has been shown. The proposed shelf-life of 36 months without any special storage condition is justified.

Specific measures for 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 MEB considers that Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection 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 Sotalol HCl Tiofarma 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. The reference product is no longer marketed in the Netherlands. Currently, there are no sotalol

products for parental administration registered in the Netherlands, only sotalol tablets. This product will substitute the products containing the same active substance and pharmaceutical form that are currently imported.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Sotacor. 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sotalol 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Sotalol HCl Tiofarma 40 mg/4 ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Discussion on the clinical aspects

IV.3.1 Therapeutic indications

Initially the MAH proposed to include the indication 'efficacy testing of the medicine during programmed electrical stimulation testing in patients with inducible ventricular and supraventricular tachyarrhythmias'. Although it is in line with the historical reference product Sotacor, the indication was not substantiated with clinical documentation in the clinical overview. Therefore this indication has been removed.
The indications are limited to 'treatment of acute ventricular arrhythmias, including life-threatening ventricular tachyarrhythmias, symptomatic non-sustained ventricular tachyarrhythmias' and 'temporary substitution for oral therapy in patients who are unable to take oral sotalol'.

IV.3.1 Paediatric dosing

The MAH discussed the paediatric dosing, acknowledging the limited sources describing paediatric sotalol IV use.

Zhang *et al.* (2012)[1] described the use of high intravenous doses of sotalol to treat incessant tachyarrhythmias in children. A total of 19 children (age 2.0 ± 2.3 years) presenting incessant tachyarrhythmias were treated with intravenous sotalol (dose 5 mg/kg/day). Of these 19 patients, 14 patients (73.3%) were successfully reversed to sinus rhythm during 24 h of intravenous sotalol.

[1] Zhang, Y., Li, X., Xu, Z., Liu, H. and Li, X. (2012). Intravenous sotalol for incessant tachyarrhythmias in children. Heart 98(Suppl. 2): E260.

Duration between start of intravenous sotalol to reversion of sinus rhythm was 5.3 ± 9.3 h (0.05–24 h). In this paper it was concluded that intravenous sotalol can be safely and effectively used for paediatric tachyarrhythmias with normal cardiac function. In addition, no intravenous sotalol associated arrhythmias or toxicity were detected. Monitoring of QTc was deemed necessary during treatment with intravenous sotalol.

The FDA labelling states an advised paediatric dose which is comparable to their adult dose based on pharmacokinetic data. The rationale being that since the Class III antiarrhythmic potency in children is not considered very different from that in adults, reaching plasma concentrations that occur within the adult dose range is an appropriate guide. Using the same rationale, the MAH proposed a dose of 1.2 mg/kg day (equivalent to 45 mg/m^2/day), which is comparable to the accepted dose in many sotalol SmPCs in adults (80 mg total oral dose).

As sotalol is nearly completely absorbed after oral administration and undergoes essentially no first-pass hepatic metabolism, approximately similar exposure is expected after IV or oral application.
Reference is made to a study by Laër *et al*. (2005)[2]. The objective of this study was to develop age-specific dosage guidelines for sotalol in children with supraventricular tachycardia based on a population pharmacokinetic covariate analysis, clinical trial simulations and pharmacodynamics. Sotalol was administered orally. Seventy-six patients were subcategorized into neonates (1-28 days, n=12), infants and toddlers (29 days to 23 months, n=12), children (2-12 years, n=26) and adolescents (13 to 17 years, n=5). The study showed that inter-individual difference in oral clearance and volume of distribution could largely be attributed to size and weight differences, with an additional age effect on clearance in children younger than one year. The additional age effect can be explained by the fact that clearance of sotalol follows the maturation process of renal function in developing children with higher drug exposure in neonates and young infants.
Based on the results, Laër *et al*. list the following dosing recommendations derived from different age groups: 2 and 4 mg/kg/day for neonates, 3 and 6 mg/kg/day for infants and children <6 years and 2 and 4 mg/kg/day for children > 6 years, with an 8h-dosing interval.

The proposed posology for Sotalol HCl Tiofarma solution for injection, 1.2 mg/kg to 5 mg/kg per day IV for children aged 2 years and older, is approximately in the same range as the dosing recommendations of the study by Laër *et al.* (2 to 6 mg/kg per day orally).
Furthermore, the dose recommendation of the Dutch Paediatric Formulary (*Kinderformularium*) for IV sotalol is 0.2-1.5 mg/kg/dose for the paediatric population of 1 month – 18 years. This is also mainly based the consensus opinion of paediatric cardiologists and paediatric intensivists that paediatric posology can be extrapolated from the dose used in adults. The SmpC states that individualization of dosage is required in children under the age of 2 years. Sotalol elimination is predominantly via the kidney. As renal function is developing in children younger than 2 years, drug exposure is greater than in children older than 2 years.

IV.3.1 Conclusion

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sotacor. No new clinical studies were conducted. The MAH demonstrated equivalence to the reference product based on chemical-pharmaceutical data.
The proposed posology, based on the rationale that the paediatric posology can be extrapolated from the dose used in adults, is acceptable. The MAH proposed to include paediatric dosing in section 4.2 of the SmpC. However, the current posology is not based on clinical studies, but mainly derived from pharmacokinetic data. In addition, there is no explicit paediatric indication in section 4.1. Therefore the MEB concluded that paediatric dosing information should be presented in section 5.2 of the SmPC. In accordance with the SmPC guideline, a statement is included in section 4.2 that relevant paediatric data are presented in section 5.2.

[2] Läer S, Elshoff J-P, Meibohm B, Weil J, Mir TS, Zhang W, et al. (2005). Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. J Am Coll Cardiol 46: 1322–1330.

IV.1 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 Sotalol HCl Tiofarma.

- Summary table of safety concerns as approved in RMP

Important identified risks	Proarrhythmia and cardiac failure Drug-drug interactions with antiarrhythmic drugs
Important potential risks	-
Missing information	Gender differences

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

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 test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Sotacor, solution for injection 10 mg/ml. Sotacor is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 has therefore granted a marketing authorisation. Sotalol HCl Tiofarma 40 mg/4 ml, solution for injection was authorised in the Netherlands on 2 June 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse