

SOTALOL 80 MG AND 160 MG TABLETS

PL 15922/0018

PL 15922/0022

UKPAR

TABLE OF CONTENTS

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 17
Summary of product characteristics	Page 18
Product information leaflet	Page 39
Labelling	Page 41

SOTALOL 80 MG AND 160 MG TABLETS

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Apotex Europe Limited Marketing Authorisations (licences) for the medicinal products Sotalol 80 mg and 160 mg Tablets (Product Licence numbers: 15922/0022 and 15922/0018, respectively). These medicines are only available with a prescription.

Sotalol tablets are beta blockers, which means that they block the beta receptors that are present on many organs of the body, including the heart. Blocking these receptors on the heart slows the heart rate and causes the heart to beat with less force.

Sotalol 80 mg and 160 mg Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

SOTALOL 80 MG AND 160 MG TABLETS

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PL 15922/0022

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 11
Clinical assessment (including statistical assessment)	Page 12
Overall conclusions and risk benefit assessment	Page 16

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Sotalol 80 mg and 160 mg Tablets to Apotex Europe Limited on 4 January 2007. These are prescription-only medicines (POM).

These are national applications submitted under Article 10.1 of Directive 2001/83, claiming essential similarity to Sotacor Tablets 80 mg (PL 00125/0076) and 160 mg (PL 00125/0093), granted to Bristol Myers on 4 July 1974 and 9 June 1976, respectively.

Sotalol 80 mg and 160 mg Tablets are indicated for the treatment of life-threatening ventricular tachyarrhythmias and symptomatic non-sustained ventricular tachyarrhythmias. These tablets can also be used in the prevention of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, and paroxysmal A-V re-entrant tachycardia using accessory pathways. Sotalol 80 mg and 160 mg Tablets can be used in the prevention of paroxysmal supraventricular tachycardia after cardiac surgery; they can also be used to maintain a normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

PHARMACEUTICAL ASSESSMENT

I INTRODUCTION AND BACKGROUND

These are national abridged applications for Marketing Authorisations for Sotalol 80 mg and 160 mg Tablets, submitted under Article 10.1 of EC Directive 2001/83, as amended. The applicant is claiming 'essential similarity' to Sotacor Tablets 80 mg and 160 mg, granted to Bristol Myers Pharmaceuticals in the UK.

In the UK, Product Licences numbers PL 00125 /0076 and 00125/0093 were first granted to Bristol Myers on 4 July 1974 and 9 June 1976, respectively.

Sotalol hydrochloride is non-cardioselective beta blocker. It is reported to lack both intrinsic sympathomimetic and membrane-stabilising properties. In addition to the class II antiarrhythmic activity of beta blockers, sotalol lengthens the duration of the action potential, resulting in class III antiarrhythmic activity.

Sotalol is used in the management of ventricular and supraventricular arrhythmias. The suggested initial dose of sotalol hydrochloride is 80 mg daily by mouth, given as a single or in two divided doses. The dose should be adjusted to achieve steady state, usually achieved with doses of 160 to 320 mg daily (given in two divided doses). Some patients may require doses as high as 480-640 mg daily. The proposed indications and dose are consistent with those licensed for Sotacor tablets in the UK.

II PHARMACEUTICAL ASSESSMENT

1. DRUG SUBSTANCE

The active ingredient, sotalol hydrochloride, is the subject of a Ph Eur monograph and the specification provided by the applicant complies with this monograph. A satisfactory Certificate of Suitability has been provided.

2. FINISHED PRODUCT

IIA COMPOSITION

The qualitative composition of the proposed 80 mg and 160mg tablets is given as follows:

Name of Ingredient	Function	Reference standard
<u>Active Substance</u>		
Sotalol Hydrochloride	Active	Ph Eur

<u>Excipients</u>		
Dextrates (hydrous)	Diluent	NF
Methylcellulose	Binding agent	Ph Eur
Magnesium stearate	Lubricant	Ph Eur
Colloidal silicon dioxide	Glidant, absorbant/adherent	Ph Eur
Indigotine Al. Lake E132	Colouring agent	HSE

Formulation used in Bioavailability Study

The formulation used in the bioequivalence study is identical to that proposed for marketing, although that the drug substance was sourced from a different supplier. The finished product used in the study was made by the proposed finished product manufacturer.

Development Pharmaceutics

Sotalol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations are obtained about 2 to 4 hours after dosing. The plasma elimination half-life is about 10 to 20 hours. Very little sotalol is metabolised and it is excreted unchanged in urine. Binding to plasma proteins is reported to be low. It crosses the placenta and is distributed into breast milk, where higher concentrations have been achieved than in maternal serum. Sotalol is removed by dialysis. Food reduces the bioavailability of the drug.

The objective of the development was to produce generic alternatives to the innovator products available in the UK, such as Sotacor tablets 80 mg and 160mg.

The development pharmaceutics was fairly well presented and the issues addressed included the rationale for the formulation. Development studies on the manufacturing process were provided. Chemical and physical compatibility were demonstrated in the course of the finished product stability studies.

Comparative dissolution profiles were provided of the innovator's 160 mg tablet from France (Sotalax) ,used in the bioavailability study, and the proposed 160 mg product (table 3). The dissolution profiles were very similar and these products were subsequently shown to be bioequivalent.

Dissolution between two batches of each strength of the proposed products was also compared with one batch of each strength of the UK brand leader. The results showed comparable profiles after 20 minutes.

The source of drug substance intended for commercial product differs from that used in the pivotal bioequivalence study batch. Comparative dissolution profiles have been provided for batches manufactured using both sources of drug substance and these justify the proposed commercial drug substance manufacturer.

The dissolution methodology chosen to evaluate the dissolution profiles is the proposed dissolution method for the finished product given.

The applicant has demonstrated chemical similarity for the proposed tablets by undertaking a comparison of the impurity profile of the proposed products together with the UK reference product. A suitable method has been used to compare the impurities between generic and originator products.

IIB METHOD OF MANUFACTURE

Satisfactory evidence of GMP for the manufacturing site has been provided in the form of the GMP certificate. A satisfactory manufacturing formula for the maximum batch size has been provided. The manufacturing process has been described and a satisfactory flow diagram has been presented.

In-process controls have been adequately described. The controls are considered appropriate for this type of product.

Process validation data are provided in support of the manufacturing process and demonstrate consistent manufacture at a scale representative of the commercial batch size.

Data reported for the in-process parameters and the finished products indicate compliance with the defined in-process and finished product specifications and the general Ph.Eur requirements of the tablets.

IIC CONTROL OF STARTING MATERIALS

Excipients

The excipients conform to the necessary requirements. A certificate of analysis for each excipient has been provided and these are satisfactory. A number of the test limits are tighter than those in the appropriate pharmacopoeial monograph. Details of the routine tests to be carried out upon receipt of each excipient and their frequency as undertaken by the finished product manufacturer are provided.

A statement has been provided indicating that the magnesium stearate complies with the CPMP guideline from 22 October 1998 'Note for guidance on Minimising the Risk of Transmitting Animal spongiform Encephalopathy Agents via Medicinal Products'.

The applicant has also provided a current TSE certificate for magnesium stearate, which is deemed acceptable.

Packaging Materials

The packaging specified for these products are blisters of PVC/PVDC/Aluminium with PVC/PVAC coating.

The specifications for the packaging materials are provided and are satisfactory. Details of routine tests are according to the specifications given. A certificate of analysis for the PVC/PVDC film and the plain foil has been provided.

Satisfactory confirmation of the plastic components' compliance with Directive 90/128/EEC, as amended, is provided. This is acceptable.

IID CONTROL TESTS ON THE INTERMEDIATE PRODUCT

Not applicable.

III CONTROL TESTS ON THE FINISHED PRODUCT

The control tests on the finished products have been detailed. The limits proposed apply at release and for the shelf life of the product.

The control tests and limits proposed for the tablets are satisfactory.

The tablets, in addition, comply with the BP 1999 monograph for Sotalol tablets.

Satisfactory certificates of the reference standards used are provided. Batch analyses have been provided for batches of both strengths. All batches show conformance with the specification, with the exception of the dye identification test which was not included in the specification at that time. This was undertaken subsequently on three other batches of 80 mg tablets and compliance was demonstrated.

IIIF STABILITY

Drug Substance

The certificate of suitability confirms the stability of the drug substance over its re-test interval.

Finished Product

Finished product stability data for both strengths of tablets support the proposed shelf life of 36 months with storage conditions of 'Do not store above 25°C. Store in the original package. Keep package in the outer carton'. This is satisfactory.

Sotalol hydrochloride is light sensitive. The photostability of the product has not been presented and the products are to be packed in clear blisters. However, a general storage statement advising protection from light using the words from CPMP/QWP/609/96 (Store in the original package. Keep package in the outer carton) has been provided in the MAA, SPC, PIL and labels and this is acceptable.

BIOAVAILABILITY/BIOEQUIVALENCE

The bioavailability study was presented in the clinical dossier. A single dose, randomised 3-way cross-over bioequivalence study was undertaken, comparing the proposed 160 mg product with two reference 160mg tablets from France (Sotalex, Bristol Myers Squibb, France) and Australia (Sotacor, Bristol Myers Squibb, Australia) in healthy adult male volunteers under fasting conditions. Twenty seven volunteers started the study and there were no withdrawals. There was no pre-study power statement, although the inclusion of 27 subjects is acceptable. A post-study statement is made that there was >99.9% power to detect a 20% difference at the 5% level. Certificates of analysis for the three products used in the biostudy are provided.

The study was undertaken in 1997 and the three treatment phases were separated by a washout period of 7 days. The half life of sotalol is about 10-20 hours. Therefore, the 7 day washout period is acceptable. Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 60 hours post dose in each period.

The pharmacokinetic parameters determined were $AUC_{0-\infty}$, AUC_{0-t} , C_{max} , t_{max} , elimination constant (kel) and half-life. The pharmacokinetic parameters are summarised in Table 6.

Table 6: Summary of Pharmacokinetic Data

Parameter	Proposed Sotalol tablet 160mg Mean (CV) A	Sotalex-French Reference tablet 160mg Mean (CV) B	Sotacor-Australian Reference tablet 160mg Mean (CV) C	Ratio A/B (90% Confidence interval)	Ratio A/C (90% Confidence interval)
Ln $AUC_{0-\infty}$ (ng.h/ml)	16143.59 (12.8)	15205.58 (20.2)	16248.22 (14.5)	101.7-110.8	95.2-103.7
Ln C_{max} (ng/ml)	1335.09 (17.6)	1212.09 (28.7)	1305.80 (22.4)	103.0-117.8	95.6-109.3
T_{max} (h)	3.093 (33.3)	3.113 (27.9)	3.056 (33.5)	-	-
Ln AUC_{0-t} (ng h/ml)	15555.11 (13.3)	14542.63 (21.5)	15595.44 (15.2)	102.1-112.0	95.2-104.5
Kel (1/h)	0.07273 (18.3)	0.07033 (21.6)	0.07082 (20.1)	-	-
$t_{1/2}$ (h)	9.838 (18.2)	10.285 (20.8)	10.200 (21.7)	-	-

The 90% confidence intervals for $AUC_{0-\infty}$, AUC_{0-t} and C_{max} were within the normally accepted criteria of 80-125% for log transformed data to demonstrate bioequivalence.

This is acceptable, although the range for all three parameters for the A/B ratio did not include 100%.

The guidelines on bioavailability studies recommends that the highest dose in the tablet range proposed for marketing is studied, i.e. the 160mg tablet, as has been undertaken in this bioavailability study. The formulation of the proposed 160 mg tablet is dose proportional to the 80 mg tablets. The dissolution is rapid for both strengths and comparable to the French Sotalol tablets 160 mg. The formulation of the UK and French innovator products is not similar, but this is not thought to be of any consequence for a water soluble drug and is unlikely to affect the release of the drug. Therefore, in view of the fact that the dissolution is similar between the UK and French innovator products and both strengths of the proposed tablets, the study is acceptable.

Full details of the analytical method used to determine the sotalol in plasma and the validation of the method in conformance with ICH guidelines are provided.

3. PRODUCT PARTICULARS

Product Name

The generic name, Sotalol 80 mg and 160mg Tablets, is proposed and is acceptable.

Summary of Product Characteristics (SPC)

The SPC for this product is satisfactory.

Patient Information Leaflet (PIL) and labels

The PIL for this product is satisfactory.

Marketing Authorisation Application (MAA)

The MAA form submitted with this application is satisfactory.

Expert Report

The pharmaceutical expert report has been signed by a suitably qualified expert. It provides a reasonable summary of the data. A satisfactory CV is included.

III PHARMACEUTICAL CONCLUSIONS

Therefore, there is no objection to the grant of UK Marketing Authorisations for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is an abridged application for a marketing authorisation for two strengths of sotalol hydrochloride made under Article 10.1 of EC Directive 2001/83. The applicant claims essential similarity to Sotacor Tablets (Bristol-Myers Pharmaceuticals), which has been authorised and marketed continuously for more than 10 years in the EU (licensed 4 January 1974).

2. BACKGROUND

Sotalol is a non-selective hydrophilic, adrenergic receptor blocker, devoid of intrinsic sympathoimetic or membrane-stabilising activity.

3. INDICATIONS

1. Treatment of life-threatening ventricular tachyarrhythmias.
2. Treatment of symptomatic non-sustained ventricular tachyarrhythmias.
3. Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways.
4. Prophylaxis of paroxysmal supraventricular tachycardia after cardiac surgery.
5. Maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

The claimed indications are identical to those of the referenced licensed product. The indications are supported by the data and bibliographic evidence submitted.

4. DOSE & DOSE SCHEDULE

Posology

Medical evaluation, including ECG control with measurement of the correct QT intervals is required before initiating treatment and in dose adjustment. Therefore, treatment with sotalol is recommended in a facility capable of monitoring and assessing cardiac rhythm. Proarrhythmic events can occur at therapy initiation and when a dose is increased (see section 4.4, Special warnings and precautions for use). Due to sotalol's beta-adrenergic blocking properties, treatment should not be discontinued suddenly, especially in patients with ischaemic heart disease (angina pectoris, prior acute myocardial infarction) or hypertension, to prevent exacerbation of the disease (see section 4.4, Special warnings and precautions for use).

Adults:

Initial dose of 80 mg as a single or in two divided doses. Usual daily dose of 160-320 mg in two divided doses at 12 hour intervals. Adjustment of dose should be gradual allowing 2-3 days between dosing increments in order to achieve steady-state, and to allow monitoring of QT intervals.

Daily doses of 480-640mg may be required for patients with life-threatening refractory ventricular arrhythmias, under specialist supervision. To be prescribed only when the potential benefits outweigh the increased risk of adverse events, particularly proarrhythmias (see section 4.4, Special warnings and special precautions for use).

Children:

Not intended for use.

Renal Impairment:

Dose to be adjusted according to creatinine clearance.

<u>Creatine clearance (ml/min)</u>	<u>Dose</u>
>60	Recommended sotalol dose
30-60	½ recommended sotalol dose
10-30	¼ recommended sotalol dose
<10	Not recommended.

Creatinine clearance can be estimated from serum creatinine by the Cockcroft and Gault formula:

Men: $\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$

Women: idem x 0.85

N.B. 1 mg/dl = 88.4 µmd/1.

Hepatic Impairment:

No dose adjustment is required.

Method of Administration:

Oral.

The dose and dose schedule is satisfactory.

5. TOXICOLOGY

No new toxicological data were submitted. The pre-clinical pharmacology of the active remains satisfactory.

6. CLINICAL PHARMACOLOGY

The applicant submitted a bioequivalence study.

Aim

To assess oral bioequivalence between the test 160mg Sotalol Tablet preparation and two comparators - 160mg Sotalex (France) and Sotacor (Australia) reference products (BMS, identical to Sotacor (UK)).

Design and Methods

The study was conducted in compliance with Good Clinical Practice. Twenty-seven healthy male volunteers were randomised to take each preparation as a single 160mg oral dose, separated by a washout period of seven days. Fluid and food were appropriately restricted and medication was taken following an overnight fast with 240 ml tap water. Venous blood samples were taken pre-dose and up to 60 hours following each medication. Sotalol was measured by HPLC with fluorescence detection with a lower limit of quantification of 30ng/ml.

Results

All 27 subjects completed the study. There were no dropouts. Only results with the EU comparator Sotalex are shown.

Summary of Pharmacokinetic Data for Sotalol

Variable	Unit	(Reference) Geometric Mean SD	(Test) Geometric Mean SD	Mean Ratio (%)*	90% Confidence interval (%)**	Intra- individual CV (%)
Cmax	(ng/ml)	1212.1	1335.1	110.1	103.0-117.8	
AUC	(ng.h/ml)	15205.6	16143.6	106.2	101.7-110.8	
t _{1/2}	(h)	10.3	9.8	-	-	

* Point estimate of “test/reference” mean ratio from analysis of variance of log-transformed data.

** 90% Conventional confidence interval for the “test/reference” mean ratio analysis of variance of log-transformed data.

Assessor’s comment

The data show that the two products are bioequivalent. Since the original product’s licence was granted more than ten years ago and it has been continually marketed since that time within the EU, and is marketed in the UK, the applicant is able to claim essential similarity for all indications of the originator.

7. EFFICACY

No new efficacy data were submitted by the applicant. The applicant has provided sufficient bibliographic data to support the conclusions. The documented clinical efficacy of the active remains satisfactory for the claimed indications and at the proposed dosages.

8. SAFETY

No new safety data were submitted with the application. The recorded safety profile of the active remains satisfactory when used in the claimed indications and at the recommended dosages. Safety findings in the bioequivalence study were those

associated with the drug's use - and were similar and of comparable intensity to the reference product.

9. EXPERT REPORTS

The expert reports on the pharmaco-toxicological and clinical aspects of the products proposed for marketing are written by independent experts with appropriate qualifications.

10. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC for this product is satisfactory.

11. PATIENT INFORMATION LEAFLET

The PIL for this product is satisfactory.

12. LABELLING

All labelling is satisfactory.

13. APPLICATION FORM

This conformed with EC requirements and was satisfactory.

14. DISCUSSION

Provided that the quality of the products is satisfactory, the applicant has provided sufficient data to conclude essential similarity to the cross-referenced product, Sotacor tablets 80 mg and 160 mg, under Article 10.1 of EC Directive 2001/83. The documentation provided in the application complies with the regulations and is satisfactory.

15. CONCLUSION

A product licence should be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Sotalol 80 mg and 160 mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY AND SAFETY

The efficacy data submitted for this product are satisfactory.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Sotalol 80 mg and 160 mg Tablets. The risk benefit is therefore considered to be positive.

SOTALOL 80 MG AND 160 MG TABLETS

PL 15922/0018

PL 15922/0022

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 27 March 2000.
2	Following assessment of the application the MHRA requested further information relating to the dossier on 17 July and 17 August 2000
3	The applicant responded to the MHRA's requests, providing further information on the dossier on 17 May 2001
4	Following assessment of the response the MHRA requested further information relating to the dossier on 5 June 2001
5	The applicant responded to the MHRA's requests, providing further information on the dossier on 21 June 2006
6	Following assessment of the response the MHRA requested further information relating to the dossier on 19 November 2001
7	The applicant responded to the MHRA's requests, providing further information on the dossier on 10 December 2001
8	Following assessment of the response the MHRA requested further information relating to the dossier on 22 February 2002
9	The applicant responded to the MHRA's requests, providing further information on the dossier on 4 December 2002
10	Following assessment of the response the MHRA requested further information relating to the dossier on 6 June 2003
11	The applicant responded to the MHRA's requests, providing further information on the dossier on 21 February 2006 and 21 November 2006
12	The application was determined on 4 January 2007

SUMMARY OF PRODUCT CHARACTERISTICS

Sotalol 80 mg Tablets:

1 NAME OF THE MEDICINAL PRODUCT

Sotalol 80 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of sotalol hydrochloride.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Oblong, blue tablet engraved 'APO-80' on one side and scored on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of life-threatening ventricular tachyarrhythmias.

Treatment of symptomatic non-sustained ventricular tachyarrhythmias.

Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways.

Prophylaxis of paroxysmal supraventricular tachycardia after cardiac surgery.

Maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

4.2 Posology and method of administration

Posology

Medical evaluation, including ECG control with measurement of the correct QT intervals is required before initiating treatment and in dose adjustment. Therefore, treatment with sotalol is recommended in a facility capable of monitoring and assessing cardiac rhythm. Proarrhythmic events can occur at therapy initiation and when a dose is increased (see section 4.4, Special warnings and precautions for use).

Due to sotalol's beta-adrenergic blocking properties, treatment should not be discontinued suddenly, especially in patients with ischaemic heart disease (angina pectoris, prior acute myocardial infarction) or hypertension, to prevent exacerbation of the disease (see section 4.4, Special warnings and precautions for use).

Adults

Initial dose of 80 mg as a single or in two divided doses. Usual daily dose of 160-320 mg in two divided doses at 12 hour intervals. Adjustment do dose should be gradual allowing 2-3 days between dosing increments in order to achieve steady-state, and to allow monitoring of QT intervals.

Daily doses of 480 – 640 mg may be required for patients with life-threatening refractory ventricular arrhythmias, under specialist supervision. To be prescribed only when the potential benefits outweigh the increased risk of adverse events, particularly proarrhythmias (see section 4.4, Special warnings and special precautions for use).

Children

Not intended for use.

Renal Impairment

Dose to be adjusted according to creatinine clearance

<u>Creatinine clearance</u> (ml/min)	<u>Dose</u>
>60	Recommended sotalol dose
30 - 60	½ recommended sotalol dose
10 - 30	¼ recommended sotalol dose
<10	Not recommended

Creatinine clearance can be estimated from serum creatinine by the Cockcroft and Gault Formula:

Men:
$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Women: as above x 0.85

N.B. 1 mg /dl = 88.4 micromol/l.

Hepatic Impairment:

No dose adjustment is required.

Method of Administration:

Oral.

4.3 Contraindications

Patients known to be hypersensitive to sotalol hydrochloride or any of the excipients.

Sotalol should not be administered to patients with:

evidence of sick sinus syndrome
second and third degree AV heart block (unless a functioning pacemaker is present)
congenital or acquired long QT syndromes
torsades de pointes
symptomatic sinus bradycardia
uncontrolled congestive heart failure
cardiogenic shock
anaesthesia that produces myocardial depression
untreated phaeochromocytoma
hypotension (except due to arrhythmia)
Raynaud's phenomenon and severe peripheral circulatory disturbances
history of chronic obstructive airway disease or bronchial asthma
metabolic acidosis
renal failure (creatinine clearance <10 ml/min)

4.4 Special warnings and precautions for use

The following conditions require special consideration:

abrupt withdrawal
proarrhythmias
electrolyte disturbances
congestive heart failure
recent MI
electrocardiographic changes
anaphylaxis
anaesthesia
diabetes mellitus
thyroxicosis
renal impairment
psoriasis

Abrupt withdrawal

Hypersensitivity to catecholamines is observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias, and in some cases myocardial infarction have been reported after abrupt discontinuation of therapy. Patients should be carefully monitored when discontinuing chronically administered sotalol, particularly those with ischaemic heart disease. If possible the dosage should be gradually reduced over a period of one to two weeks, if necessary at the same time initiating replacement therapy. Abrupt discontinuation may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmias

The most dangerous adverse effect of Class I and III antiarrhythmic drugs such as sotalol is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. Drugs that prolong the QT-interval may cause torsades de points, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of torsades de points is associated with the prolongation of the QT-interval, reduction of the heart rate, reduction in serum potassium and magnesium, high plasma sotalol concentrations and with the concomitant use of sotalol and other medications which have been associated with torsades de points (see section 4.5, Interactions with other medicinal products and other forms of interaction).

Females may be at risk of developing torsades de points.

The incidence of torsades de points is dose dependent. Torsades de points usually occurs early after initiating therapy or escalation of the dose and can progress to ventricular fibrillation.

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (torsades de points or new sustained VT/VF) was <2% at doses up to 320 mg. The incidence more than doubled at higher doses.

Other risk factors for torsades de points were excessive prolongation of the QT_C and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure have the highest risk of serious proarrhythmia (7%). Proarrhythmic events must be anticipated not only on initiating therapy but with every upward dose adjustment. Initiating therapy at 80 mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol caution should be used if the QT_C exceeds 500 msec whilst on therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QT_C-interval exceeds 550 msec. Due to the multiple risk factors associated with torsades de points, however, caution should be exercised regardless of the QT_C-interval.

Electrolyte disturbances

Sotalol should not be used in patients with hypokalaemia or hypomagnesaemia prior to correction of imbalance; these conditions can exaggerate the degree of QT prolongation, and increase the potential for torsades de points. Special attention

should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhoea or patients receiving concomitant magnesium- and/or potassium-depleting drugs.

Congestive heart failure

Beta-blockade may further depress myocardial contractility and precipitate more severe heart failure. Caution is advised when initiating therapy in patients with left ventricular dysfunction controlled by therapy i.e. ACE inhibitors; diuretics; digitalis; etc.; a low initial dose and careful dose titration is appropriate.

Recent MI

In post-infarction patients with impaired left ventricular function, the potential benefits against risks must be considered before administering sotalol. Careful monitoring and dose titration are critical during initiation and follow-up therapy. Sotalol should be avoided in patients with left ventricular ejection fractions $\leq 40\%$ without serious ventricular arrhythmias.

Electrocardiographic changes

Excessive prolongation of the QT-interval can indicate toxicity and should be avoided (see Proarrhythmias). Bradycardia increases the risk of torsades de pointes.

Anaphylaxis

Patients with a history of anaphylactic reaction to various allergens may experience a more severe reaction on repeated challenge while taking beta-blockers. Administration of adrenaline at the usual doses to treat the allergic reaction may not be adequate.

Anaesthesia

Sotalol should be used with caution in patients undergoing surgery and in association with anaesthetics that cause myocardial depression, such as cyclopropane or trichlorethylene.

Diabetes mellitus

Sotalol should be used with caution in patients with diabetes, especially labile diabetes or with a history of episodes of spontaneous hypoglycaemia, as beta-blockade may mask some important signs of the onset of acute hypoglycaemia e.g. tachycardia.

Thyrotoxicosis

Beta-blockade may mask certain clinical signs of hyperthyroidism such as tachycardia. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm.

Renal impairment

Sotalol is mainly eliminated by the kidneys. Dose adjustment is required (see section 4.2, Posology and method of administration).

Psoriasis

Beta-blocking drugs have been reported rarely to exacerbate the symptoms of psoriasis vulgaris.

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics

Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness (see section 4.4, Special warnings and special precautions for use). The concomitant use of other beta-blocking agents with sotalol may result in additive Class II effects.

Other drugs prolonging the QT-interval

Sotalol should be given with extreme caution in conjunction with other drugs known to prolong the QT-interval such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole. Other drugs that have been associated with an increased risk of torsades de pointes include vincamine, fenoxedil, erythromycin IV, halofantrine, pentamidine and sultopride.

Floctafenine

Beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Calcium channel blocking drugs

Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers such as verapamil and diltiazem because of the additive effect on atrioventricular conduction, and ventricular function.

Potassium-depleting diuretics

Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsades de pointes (see section 4.4, Special warnings and special precautions for use).

Other potassium-depleting drugs

Amphotericin B (IV route), corticosteroids (systemic administration), and some laxatives may also be associated with hypokalaemia; potassium levels should be monitored and corrected appropriately during concomitant administration with sotalol.

Clonidine

Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, the beta-blocker should be discontinued slowly several days before the gradual withdrawal of clonidine.

Digitalis glycosides

Single and multiple doses of sotalol do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol treated patients also receiving digitalis glycosides; however, this may be related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digitalis glycosides. Association of digitalis glycosides with beta-blockers may increase auriculo-ventricular conduction time.

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting drugs, such as reserpine, guanethidine, or alpha methyl dopa, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients should be closely monitored for evidence of hypotension and/or marked bradycardia which may produce syncope.

Insulin and oral hypoglycaemics

Hyperglycaemia may occur, and the dosage of antidiabetic drugs may require adjustment. Symptoms of hypoglycaemia (tachycardia) may be masked by beta-blocking agents.

Neuromuscular blocking agents like tubocurarine

The neuromuscular blockade is prolonged by beta-blocking agents.

Beta-2-receptor stimulants

Patients in need of beta-agonists should not normally receive sotalol. However, if concomitant therapy is necessary beta-agonists may have to be administered in increased dosages.

Drug/laboratory interaction

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by photometric methods. Patients suspected of having pheochromocytoma and who are treated with sotalol should have their urine screened utilising the HPLC assay with solid phase extraction.

4.6 Pregnancy and lactation

In animal studies, sotalol did not produce teratogenic effects or any other harmful effects on the foetus. Despite the absence of adequate and well-controlled studies in pregnant women, sotalol has been shown to cross the placenta and is found in amniotic fluid. Beta-blocking drugs reduce placental perfusion, which may result in intrauterine foetal death, immature and premature births. Adverse effects, such as hypoglycaemia and bradycardia may occur in foetus and neonates. In addition, neonates in the post-natal period are at increased risk of cardiac and pulmonary complications. Therefore the potential benefits against the risks must be considered before administering. If maternal therapy cannot be interrupted for 2-3 days before day of birth, the neonate needs careful monitoring for 48-72 hours following the birth.

Breast-feeding is not recommended during treatment with sotalol, as most beta-blocking drugs will be excreted into breast milk

4.7 Effects on ability to drive and use machines

There are no data to suggest that sotalol affects the ability to drive and use machines. Consideration should be given to the possible side-effects of dizziness and fatigue (see section 4.8, Undesirable effects).

4.8 Undesirable effects

The most frequent adverse effects of sotalol arise from its beta-blockade properties. They are usually transient and consequently suspending or withdrawing treatment is rarely necessary, however a decrease in dose may be required. The most significant adverse effects are those due to proarrhythmia, including torsades de pointes (see section 4.4, Special warnings and special precautions for use).

Adverse events occurring in 1% or more patients:

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, rashes, cramps, fever, taste abnormalities, visual and hearing disturbances. Undesirable effects attributed to the nervous system have been reported: fatigue, dizziness, asthenia, light-headedness, headache, sleep disturbances, depression, paraesthesia, mood changes and anxiety.

Adverse events relating to the cardiovascular system include bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure and presyncope.

In addition, sexual dysfunction may occur.

In clinical trials, adverse events leading to discontinuation of sotalol in patients with cardiac arrhythmia were:

fatigue 4%

bradycardia (<50 bpm) 3%

dyspnoea 3%

proarrhythmia 2%

asthenia 2%

dizziness 2%

Cold and cyanotic extremities, Raynaud's phenomenon, increase in existing intermittent claudication and dry eyes have been seen in association with other beta-blockers.

4.9 Overdose

Symptoms of overdose are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia. Symptoms from massive overdose (2 - 16 g) include hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia and torsades de points.

Treatment of overdose: therapy with sotalol should be discontinued and the following therapeutic measures are to be taken, if required:

Bradycardia: Atropine (0.5 to 2mg IV), another anticholinergic drug, a beta-adrenergic agonist (isoprenaline, 5 micrograms per minute, up to 25 micrograms, by slow IV injection) or transvenous cardiac pacing.

Heart block (second and third degree): Transvenous cardiac pacing.

Hypotension: Adrenaline rather than isoprenaline or noradrenaline may be useful, depending on associated factors.

Bronchospasm: Aminophylline or aerosol beta-2-receptor stimulant.

Torsades de pointes: DC cardioversion, transvenous cardiac pacing, adrenaline and/or magnesium sulphate.

Deaths from overdose are rare.

Haemodialysis will lead to a large reduction in plasma levels of sotalol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DL-Sotalol is a non-selective hydrophilic beta-adrenergic receptor blocking agent. It is devoid of intrinsic sympathomimetic activity or membrane stabilising 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 QT_C (QT corrected for heart rate) intervals with no significant alteration in the QRS duration.

The d- and l-isomers 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 beta-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 beta-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. Twenty-four-hour control of blood pressure is maintained both in the supine and upright positions with a single daily dose.

5.2 Pharmacokinetic properties

The bioavailability of oral sotalol is greater than 90%, with peak plasma levels reached in 2.5 to 4 hours and steady-state attained within 2-3 days. There is very little inter-subject variability in plasma levels. Absorption is reduced by approximately 20% when administered with food. Dose proportionality with respect to plasma levels is seen for doses of 40 - 640 mg/day.

Distribution occurs in plasma and peripheral tissues. Sotalol crosses the blood brain barrier poorly, with cerebro-spinal fluid levels 10% of that in plasma. The elimination half-life is approximately 10-20 hours. Sotalol does not bind to plasma proteins. Sotalol is not metabolised.

The main route of elimination is by the kidneys, with approximately 80-90% of a dose excreted unchanged in the urine. The remaining portion is excreted in the faeces.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrates (hydrous)

Methylcellulose

Magnesium stearate

Colloidal anhydrous silica

Indigotine aluminium lake (E132)

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep package in outer carton.

6.5 Nature and contents of container

Blisters: PVC-PVDC / aluminium with PVC-PVAC coating.

Pack sizes: 28, 30, 56, 60, 84 and 90 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited

41 London Street

Reading

Berkshire RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)

Sotalol 80 mg Tablets: PL 15922/0022

Sotalol 160 mg Tablets: PL 15922/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 January 2007

Sotalol 160 mg Tablets:

1 NAME OF THE MEDICINAL PRODUCT

Sotalol 160 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 160 mg of sotalol hydrochloride.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Oblong, blue tablet engraved 'APO-160' on one side and scored on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of life-threatening ventricular tachyarrhythmias.

Treatment of symptomatic non-sustained ventricular tachyarrhythmias.

Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways.

Prophylaxis of paroxysmal supraventricular tachycardia after cardiac surgery.

Maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

4.2 Posology and method of administration

Posology

Medical evaluation, including ECG control with measurement of the correct QT intervals is required before initiating treatment and in dose adjustment. Therefore, treatment with sotalol is recommended in a facility capable of monitoring and assessing cardiac rhythm. Proarrhythmic events can occur at therapy initiation and when a dose is increased (see section 4.4, Special warnings and precautions for use). Due to sotalol's beta-adrenergic blocking properties, treatment should not be discontinued suddenly, especially in patients with ischaemic heart disease (angina pectoris, prior acute myocardial infarction) or hypertension, to prevent exacerbation of the disease (see section 4.4, Special warnings and precautions for use).

Adults

Initial dose of 80 mg as a single or in two divided doses. Usual daily dose of 160-320 mg in two divided doses at 12 hour intervals. Adjustment do dose should be gradual allowing 2-3 days between dosing increments in order to achieve steady-state, and to allow monitoring of QT intervals.

Daily doses of 480 – 640 mg may be required for patients with life-threatening refractory ventricular arrhythmias, under specialist supervision. To be prescribed only when the potential benefits outweigh the increased risk of adverse events, particularly proarrhythmias (see section 4.4, Special warnings and special precautions for use).

Children

Not intended for use.

Renal Impairment

Dose to be adjusted according to creatinine clearance

<u>Creatinine clearance</u> (ml/min)	<u>Dose</u>
>60	Recommended sotalol dose
30 - 60	½ recommended sotalol dose
10 - 30	¼ recommended sotalol dose

<10

Not recommended

Creatinine clearance can be estimated from serum creatinine by the Cockcroft and Gault Formula:

Men:
$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Women: as above x 0.85

N.B. 1 mg /dl = 88.4 micromol/l.

Hepatic Impairment:

No dose adjustment is required.

Method of Administration:

Oral.

4.3 Contraindications

Patients known to be hypersensitive to sotalol hydrochloride or any of the excipients.

Sotalol should not be administered to patients with:

evidence of sick sinus syndrome

second and third degree AV heart block (unless a functioning pacemaker is present)

congenital or acquired long QT syndromes

torsades de pointes

symptomatic sinus bradycardia

uncontrolled congestive heart failure

cardiogenic shock

anaesthesia that produces myocardial depression

untreated phaeochromocytoma

hypotension (except due to arrhythmia)

Raynaud's phenomenon and severe peripheral circulatory disturbances

history of chronic obstructive airway disease or bronchial asthma

metabolic acidosis

renal failure (creatinine clearance <10 ml/min)

4.4 Special warnings and precautions for use

The following conditions require special consideration:

abrupt withdrawal

proarrhythmias

electrolyte disturbances

congestive heart failure

recent MI

electrocardiographic changes

anaphylaxis

anaesthesia

diabetes mellitus

thyroxicosis

renal impairment

psoriasis

Abrupt withdrawal

Hypersensitivity to catecholamines is observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias, and in some cases myocardial infarction have been reported after abrupt discontinuation of therapy. Patients should be carefully monitored when discontinuing chronically administered sotalol, particularly those with ischaemic heart disease. If possible the dosage should be gradually reduced over a period of one to two weeks, if necessary at the same time initiating replacement therapy. Abrupt discontinuation may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmias

The most dangerous adverse effect of Class I and III antiarrhythmic drugs such as sotalol is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. Drugs that prolong the QT-interval may cause torsades de points, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of torsades de points is associated with the prolongation of the QT-interval, reduction of the heart rate, reduction in serum potassium and magnesium, high plasma sotalol concentrations and with the concomitant use of sotalol and other medications which have been associated with torsades de points (see section 4.5, Interactions with other medicinal products and other forms of interaction).

Females may be at risk of developing torsades de points.

The incidence of torsades de pointes is dose dependent. Torsades de pointes usually occurs early after initiating therapy or escalation of the dose and can progress to ventricular fibrillation.

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (torsades de pointes or new sustained VT/VF) was <2% at doses up to 320 mg. The incidence more than doubled at higher doses.

Other risk factors for torsades de pointes were excessive prolongation of the QT_C and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure have the highest risk of serious proarrhythmia (7%). Proarrhythmic events must be anticipated not only on initiating therapy but with every upward dose adjustment. Initiating therapy at 80 mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol caution should be used if the QT_C exceeds 500 msec whilst on therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QT_C-interval exceeds 550 msec. Due to the multiple risk factors associated with torsades de pointes, however, caution should be exercised regardless of the QT_C-interval.

Electrolyte disturbances

Sotalol should not be used in patients with hypokalaemia or hypomagnesaemia prior to correction of imbalance; these conditions can exaggerate the degree of QT prolongation, and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhoea or patients receiving concomitant magnesium- and/or potassium-depleting drugs.

Congestive heart failure

Beta-blockade may further depress myocardial contractility and precipitate more severe heart failure. Caution is advised when initiating therapy in patients with left ventricular dysfunction controlled by therapy i.e. ACE inhibitors; diuretics; digitalis; etc.; a low initial dose and careful dose titration is appropriate.

Recent MI

In post-infarction patients with impaired left ventricular function, the potential benefits against risks must be considered before administering sotalol. Careful monitoring and dose titration are critical during initiation and follow-up therapy. Sotalol should be avoided in patients with left ventricular ejection fractions ≤40% without serious ventricular arrhythmias.

Electrocardiographic changes

Excessive prolongation of the QT-interval can indicate toxicity and should be avoided (see Proarrhythmias). Bradycardia increases the risk of torsades de pointes.

Anaphylaxis

Patients with a history of anaphylactic reaction to various allergens may experience a more severe reaction on repeated challenge while taking beta-blockers. Administration of adrenaline at the usual doses to treat the allergic reaction may not be adequate.

Anaesthesia

Sotalol should be used with caution in patients undergoing surgery and in association with anaesthetics that cause myocardial depression, such as cyclopropane or trichlorethylene.

Diabetes mellitus

Sotalol should be used with caution in patients with diabetes, especially labile diabetes or with a history of episodes of spontaneous hypoglycaemia, as beta-blockade may mask some important signs of the onset of acute hypoglycaemia e.g. tachycardia.

Thyrotoxicosis

Beta-blockade may mask certain clinical signs of hyperthyroidism such as tachycardia. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm.

Renal impairment

Sotalol is mainly eliminated by the kidneys. Dose adjustment is required (see section 4.2, Posology and method of administration).

Psoriasis

Beta-blocking drugs have been reported rarely to exacerbate the symptoms of psoriasis vulgaris.

4.5 Interaction with other medicinal products and other forms of interaction

Antiarrhythmics

Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness (see section 4.4, Special warnings and special precautions for use). The concomitant use of other beta-blocking agents with sotalol may result in additive Class II effects.

Other drugs prolonging the QT-interval

Sotalol should be given with extreme caution in conjunction with other drugs known to prolong the QT-interval such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole. Other drugs that have been associated with an increased risk of torsades de pointes include vincamine, fenoxedil, erythromycin IV, halofantrine, pentamidine and sultopride.

Floctafenine

Beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Calcium channel blocking drugs

Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers such as verapamil and diltiazem because of the additive effect on atrioventricular conduction, and ventricular function.

Potassium-depleting diuretics

Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsades de pointes (see section 4.4, Special warnings and special precautions for use).

Other potassium-depleting drugs

Amphotericin B (IV route), corticosteroids (systemic administration), and some laxatives may also be associated with hypokalaemia; potassium levels should be monitored and corrected appropriately during concomitant administration with sotalol.

Clonidine

Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, the beta-blocker should be discontinued slowly several days before the gradual withdrawal of clonidine.

Digitalis glycosides

Single and multiple doses of sotalol do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol treated patients also receiving digitalis glycosides; however, this may be related to the presence of CHF, a known risk factor for proarrhythmia, in patients receiving digitalis glycosides. Association of digitalis glycosides with beta-blockers may increase auriculo-ventricular conduction time.

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting drugs, such as reserpine, guanethidine, or alpha methyl dopa, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients should be closely monitored for evidence of hypotension and/or marked bradycardia which may produce syncope.

Insulin and oral hypoglycaemics

Hyperglycaemia may occur, and the dosage of antidiabetic drugs may require adjustment. Symptoms of hypoglycaemia (tachycardia) may be masked by beta-blocking agents.

Neuromuscular blocking agents like tubocurarine

The neuromuscular blockade is prolonged by beta-blocking agents.

Beta-2-receptor stimulants

Patients in need of beta-agonists should not normally receive sotalol. However, if concomitant therapy is necessary beta-agonists may have to be administered in increased dosages.

Drug/laboratory interaction

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by photometric methods. Patients suspected of having pheochromocytoma and who are treated with sotalol should have their urine screened utilising the HPLC assay with solid phase extraction.

4.6 Pregnancy and lactation

In animal studies, sotalol did not produce teratogenic effects or any other harmful effects on the foetus. Despite the absence of adequate and well-controlled studies in pregnant women, sotalol has been shown to cross the placenta and is found in amniotic fluid. Beta-blocking drugs reduce placental perfusion, which may result in intrauterine foetal death, immature and premature births. Adverse effects, such hypoglycaemia and bradycardia may occur in foetus and neonates. In addition, neonates in the post-natal period are at increased risk of cardiac and pulmonary complications. Therefore the potential benefits against the risks must be considered before administering. If maternal therapy cannot be interrupted for 2-3 days before day of birth, the neonate needs careful monitoring for 48-72 hours following the birth.

Breast-feeding is not recommended during treatment with sotalol, as most beta-blocking drugs will be excreted into breast milk

4.7 Effects on ability to drive and use machines

There are no data to suggest that sotalol affects the ability to drive and use machines. Consideration should be given to the possible side-effects of dizziness and fatigue (see section 4.8, Undesirable effects).

4.8 Undesirable effects

The most frequent adverse effects of sotalol arise from its beta-blockade properties. They are usually transient and consequently suspending or withdrawing treatment is rarely necessary, however a decrease in dose may be required. The most significant adverse effects are those due to proarrhythmia, including torsades de pointes (see section 4.4, Special warnings and special precautions for use).

Adverse events occurring in 1% or more patients:

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, rashes, cramps, fever, taste abnormalities, visual and hearing disturbances. Undesirable effects attributed to the nervous system have been reported: fatigue, dizziness, asthenia, light-headedness, headache, sleep disturbances, depression, paraesthesia, mood changes and anxiety.

Adverse events relating to the cardiovascular system include bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure and presyncope.

In addition, sexual dysfunction may occur.

In clinical trials, adverse events leading to discontinuation of sotalol in patients with cardiac arrhythmia were:

fatigue 4%

bradycardia (<50 bpm) 3%

dyspnoea 3%

proarrhythmia 2%

asthenia 2%

dizziness 2%

Cold and cyanotic extremities, Raynaud's phenomenon, increase in existing intermittent claudication and dry eyes have been seen in association with other beta-blockers.

4.9 Overdose

Symptoms of overdose are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia. Symptoms from massive overdose (2 - 16 g) include hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia and torsades de points.

Treatment of overdose: therapy with sotalol should be discontinued and the following therapeutic measures are to be taken, if required:

Bradycardia Atropine (0.5 to 2mg IV), another anticholinergic drug, a beta-adrenergic agonist (isoprenaline, 5 micrograms per minute, up to 25 micrograms, by slow IV injection) or transvenous cardiac pacing.

Heart block (second and third degree) Transvenous cardiac pacing.

Hypotension Adrenaline rather than isoprenaline or noradrenaline may be useful, depending on associated factors.

Bronchospasm Aminophylline or aerosol beta-2-receptor stimulant.

Torsades de pointes DC cardioversion, transvenous cardiac pacing, adrenaline and/or magnesium sulphate.

Deaths from overdose are rare.

Haemodialysis will lead to a large reduction in plasma levels of sotalol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DL-Sotalol is a non-selective hydrophilic beta-adrenergic receptor blocking agent. It is devoid of intrinsic sympathomimetic activity or membrane stabilising 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 QT_C (QT corrected for heart rate) intervals with no significant alteration in the QRS duration.

The d- and l-isomers 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 beta-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 beta-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. Twenty-four-hour control of blood pressure is maintained both in the supine and upright positions with a single daily dose.

5.2 Pharmacokinetic properties

The bioavailability of oral sotalol is greater than 90%, with peak plasma levels reached in 2.5 to 4 hours and steady-state attained within 2-3 days. There is very little inter-subject variability in plasma levels. Absorption is reduced by approximately 20% when administered with food. Dose proportionality with respect to plasma levels is seen for doses of 40 - 640 mg/day.

Distribution occurs in plasma and peripheral tissues. Sotalol crosses the blood brain barrier poorly, with cerebro-spinal fluid levels 10% of that in plasma. The elimination half-life is approximately 10-20 hours. Sotalol does not bind to plasma proteins. Sotalol is not metabolised.

The main route of elimination is by the kidneys, with approximately 80-90% of a dose excreted unchanged in the urine. The remaining portion is excreted in the faeces.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrates (hydrous)
Methylcellulose
Magnesium stearate
Colloidal anhydrous silica
Indigotine aluminium lake (E132)

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep package in outer carton.

6.5 Nature and contents of container

Blisters: PVC-PVDC / aluminium with PVC-PVAC coating.

Pack sizes: 28, 30, 56, 60, 84 and 90 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited
41 London Street
Reading
Berkshire RG1 4PS

8 MARKETING AUTHORISATION NUMBER(S)

PL 15922/0018

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

04/01/2007

10 DATE OF REVISION OF THE TEXT

04/01/2007

LEAFLET**Patient Information Leaflet
SOTALOL 80 mg or 160 mg Tablets**

Please read this leaflet carefully before you start to take your medicine. This leaflet tells you some of the more important things you should know. If you want to know more, or you are not sure about anything, ask your doctor or pharmacist.

The name of your medicine is Sotalol 80 mg Tablets or Sotalol 160 mg Tablets.

1. WHAT IS IN YOUR MEDICINE?

The active ingredient in Sotalol Tablets is sotalol hydrochloride. Sotalol Tablets are available in two different strengths, 80 mg or 160 mg.

Each Sotalol 80 mg Tablet contains 80 mg of sotalol hydrochloride and also contains: dextrans (hydrous), methylcellulose, magnesium stearate, colloidal anhydrous silica and indigotine aluminium lake (E132). The tablet is oblong and blue, with the markings 'APO-80'.

Each Sotalol 160 mg Tablet contains 160 mg of sotalol hydrochloride and also contains: dextrans (hydrous), methylcellulose, magnesium stearate, colloidal anhydrous silica and indigotine aluminium lake (E132). The tablet is oblong and blue, with the markings 'APO-160'.

Sotalol Tablets are available in pack sizes of 28 tablets.

Marketing authorisation holder: Apotex Europe Ltd, 41 London Street, Reading, Berkshire RG1 4PS.

Distributed by: Apotex UK Limited, 6 Ridgeway Court, Grovebury Road, Leighton Buzzard, Bedfordshire LU7 4SF.

Manufacturer: Apotex Inc., Weston, Ontario, Canada M9L 1T9.

Manufacturer responsible for batch release: Chanelle Medical Ltd, Loughrea, Co. Galway, Ireland or Katwijk Farma BV, Archimedesweg 2, 2333 CN Leiden, The Netherlands.

2. ABOUT YOUR MEDICINE

Sotalol Tablets belong to a group of medicines called beta-adrenergic blocking agents or 'beta-blockers'.

Sotalol Tablets are used to treat or prevent variation from the normal regular rhythm of your heartbeat.

Your doctor may prescribe this medicine for a variety of conditions - please ask your doctor for information.

3. BEFORE TAKING YOUR MEDICINE

Make sure you have told your doctor if you:

- are pregnant, plan to become pregnant or are breastfeeding
- are sensitive to sotalol or any of the other ingredients in the tablets (see 'What is in your medicine?')

- know you suffer from any allergic reactions
- suffer from kidney or heart disease
- suffer from a very slow heartbeat, low blood pressure, circulatory problem of the hands or feet - gangrene, skin ulceration or discoloration at rest, pain at rest or on walking or Raynaud's phenomenon - colour change from white to blue to red on exposure to cold or vibration
- suffer from uncontrolled symptoms of a pheochromocytoma (a tumour of the adrenal gland)
- suffer from asthma or chronic bronchitis
- suffer from changes in acid/alkali balance in your body (metabolic acidosis)
- suffer from an overactive thyroid or psoriasis
- suffer from diabetes
- are taking medicines for the treatment of depression
- are to have an anaesthetic
- are taking any other medicines, obtained with or without a prescription, including antiarrhythmic drugs (such as disopyramide, quinidine, procainamide, amiodarone, bepridil), phenothiazines (such as chlorpromazine and thioridazine), terfenadine, vincamine, fenoxedil, erythromycin IV, halofantrine, pentamidine, sultopride, floctafenine, verapamil, diltiazem, amphotericin B, corticosteroids, laxatives, clonidine, digitalis glycosides, reserpine, guanethidine, methyl dopa and antidiabetic drugs such as insulin

Your doctor may test your blood for the level of potassium and magnesium before prescribing Sotalol Tablets. If you have low levels, your doctor may not prescribe this medicine for you.

If you see another doctor or go into hospital, let them know what medicines you are taking.

4. TAKING YOUR MEDICINE

Your doctor has decided the dose which is best for you. Always follow your doctor's instructions exactly, and those on the pharmacy label. If you do not understand anything, ask your doctor or pharmacist.

The initial dose of sotalol for adults is 80 mg as a



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single dose or in two divided doses. The dose may be increased to a usual dose of 160-320 mg daily in two divided doses at 12 hour intervals.

Sotalol is not usually administered to children.

These tablets should be taken as instructed: swallowed with water, before or after a meal. Your doctor should see you regularly during the first few weeks of treatment to check your response and may test your blood. Continue to take the tablets for as long as your doctor tells you. It may be dangerous to stop them without medical advice.

Have you missed a dose?

If you forget to take a dose, take another as soon as you remember and then your next dose at the usual time. Never take two doses at the same time. If you are unsure what to do, speak to your pharmacist or doctor.

Have you taken too many tablets?

If you accidentally take more than your prescribed dose, contact your nearest hospital casualty department, or tell your doctor immediately. Take any remaining tablets and the container with you.

5. POSSIBLE SIDE EFFECTS

Like many medicines, sotalol may occasionally cause side effects in some patients. These may include feeling sick (nausea), being sick (vomiting), stomach discomfort, diarrhoea, indigestion, flatulence, cramps, headache, dizziness, light-headedness, sudden fainting / collapse (syncope), chest pain, breathlessness, fever and skin rash.

You may also experience a change in regular heart beat, slow heart beat, fluid accumulation / swelling, abnormal taste, generalized weakness, low blood pressure, visual disturbances, tiredness, tingling in feet and hands (pins and needles).

Sotalol can alter the pattern of an ECG recording of your heart and your doctor may monitor this.

Depression, anxiety, difficulty in breathing, mood changes, problems with sleeping and sexual dysfunction may occur.

Sometimes, this type of medicine can cause cold and/ or blue fingers and toes, increased pain or weakness in the legs when walking, or dry eyes.

If you suffer any of these side effects and they become troublesome or continue, or you feel unwell in any other way, tell your pharmacist or doctor immediately and seek advice.

Warning: May cause dizziness and tiredness. If affected do not drive or operate machinery.

6. STORING YOUR MEDICINE

Do not use the tablets after the expiry date shown on the product packaging. The date is printed on the carton and the blister strip.

Do not store above 25°C. Keep container in the outer carton. Store in the original package.

Keep out of the reach and sight of children

REMEMBER: This medicine is for you only. Do not give this medicine to anyone else. It may harm them, even if their symptoms are the same as yours. Unless your doctor tells you to, do not keep medicines that you no longer need, give them back to your pharmacist for safe disposal.

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 **APOTEX UK LTD.**

Carton



PL 15922/0022:

Blister



Carton

