IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1151/066/001
Case No: 2069197

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, **North Ring Business Park**, **Santry**, **Dublin 9**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sotacor, 80 Milligram

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/08/2009** until **22/05/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sotacor 80mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80mg of sotalol hydrochloride.
Excipient: Lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Product imported from France:
Round biconvex, white tablets deeply scored on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ventricular arrhythmias:
- Treatment of life-threatening ventricular tachyarrhythmias;
- Treatment of symptomatic non-sustained ventricular tachyarrhythmias;

Supraventricular arrhythmias:
- Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways, and 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

The initiation of treatment or changes in dosage with SOTACOR should follow an appropriate medical evaluation including ECG control with measurement of the corrected QT interval, and assessment of renal function, electrolyte balance, and concomitant medications (see section as per IMB standard 4.4 Warnings and precautions).
As with other antiarrhythmic agents, it is recommended that SOTACOR be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm. The dosage must be individualized and based on the patient's response. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.
In view of its β-adrenergic blocking properties, treatment with SOTACOR 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 as per IMB standard 4.4 Warnings).
The following dosing schedule can be recommended:
The initial dose is 80 mg, administered either singly or as two divided doses.
Oral dosage of SOTACOR should be adjusted gradually allowing 2-3 days between dosing increments in order to attain steady-state, and to allow monitoring of QT intervals. Most patients respond to a daily dose of 160 to 320mg administered in two divided doses at approximately 12 hour intervals. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480 - 640 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias (see section as per IMB standard 4.4 Warnings).

Dosage in renally impaired patients
Because SOTACOR is excreted mainly in urine, the dosage should be reduced when the creatinine clearance is less than 60 ml/min according to the following table:

Creatinine clearance (ml/min)	Adjusted doses
> 60	Recommended SOTACOR Dose
30-60	½ recommended SOTACOR Dose
10-30	¼ recommended SOTACOR Dose
< 10	Avoid

The creatinine clearance can be estimated from serum creatinine by the Cockroft and Gault formula:
Men:

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

Women:
As above x 0.85

When serum creatinine is given in µmol/l, divide the value by 88.4 (1mg/dl = 88.4 µmol/l).

Dosage in hepatically impaired patients
No dosage adjustment is required in hepatically impaired patients.

Children
Sotacor is not intended for administration to children.

4.3 Contraindications

SOTACOR should not be used where there is 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; hypersensitivity to any of the components of the formulation; metabolic acidosis; renal failure (creatinine clearance < 10 ml/min).

4.4 Special warnings and precautions for use

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 SOTACOR, 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 antiarrhythmic drugs is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. Drugs that prolong the QT-interval may cause torsades de pointes, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of torsades de pointes 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 pointes (see section as per IMB standard 4.5: Interactions). Females may be at increased risk of developing torsades de pointes.

The incidence of torsades de pointes is dose dependent. Torsades de pointes usually occur within 7 days of initiating therapy or escalation of the dose, and terminate spontaneously in the majority of patients. Although most episodes of torsades de pointes are self-limited or associated with symptoms (e.g. syncope), they 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. SOTACOR should be used with caution if the QT_C is greater than 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: SOTACOR 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 risk versus benefit of sotalol administration must be considered. Careful monitoring and dose titration are critical during initiation and follow-up of therapy. SOTACOR should be avoided in patients with left ventricular ejection fractions ≤40% without serious ventricular arrhythmias.

Electrocardiographic Changes: Excessive prolongation of the QT-interval**,** >550 msec, can be a sign of toxicity and should be avoided (see *Proarrhythmias* above). Sinus bradycardia has been observed very commonly in arrhythmia patients receiving sotalol in clinical trials. Bradycardia increases the risk of torsades de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

Anaphylaxis: Patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge while taking beta-blockers. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

Anaesthesia: As with other beta-blocking agents, SOTACOR should be used with caution in patients undergoing surgery and in association with anaesthetics that cause myocardial depression, such as cyclopropane or trichloroethylene.

Sotacor can be administered with caution to patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the β-blocker, depending on the degree of airways resistance and the benefit derived from β-blockade.

Diabetes Mellitus: SOTACOR should be used with caution in patients with diabetes (especially labile diabetes) or with a history of episodes of spontaneous hypoglycaemia, since 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 (e.g., 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: As sotalol is mainly eliminated via the kidneys the dose should be adjusted in patients with renal impairment (see dosage).

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

Not recommended associations:
Antiarrhythmics:Class 1a antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with SOTACOR, because of their potential to prolong refractoriness (see section as per IMB standard 4.4 Special Warnings and Precautions). The concomitant use of other beta-blocking agents with SOTACOR may result in additive Class II effects.

Other drugs prolonging the QT-interval: SOTACOR 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 for torsades de pointes include erythromycin IV, halofantrine, pentamidine, and certain quinolone antibiotics such as grepafloxacin.

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 cardio depressant calcium-channel blockers such as verapamil and diltiazem because of the additive effects on atrioventricular conduction, and ventricular function.

Potassium-Depleting Diuretics: Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsade de pointes (see section as per IMB standard Special Warnings and 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 concommitant administration with SOTACOR.

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.

Precautions for Use:
Digitalis glycosides: Single and multiple doses of SOTACOR 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 methyldopa, 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 Tubocurarin: The neuromuscular blockade is prolonged by beta-blocking agents.

Take into account:
Beta-2-receptor stimulants: Beta-agonists may have to be administered in increased dosages when used concomitantly with SOTACOR.

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 phaeochromocytoma and who are treated with sotalol should have their urine screened utilizing the HPLC assay with solid phase extraction.

4.6 Pregnancy and lactation

Pregnancy: Animal studies with sotalol hydrochloride have shown no evidence of teratogenicity or other harmful effects on the foetus. Although there are no adequate and well-controlled studies in pregnant women, sotalol hydrochloride has been shown to cross the placenta and is found in amniotic fluid. Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia) may occur in foetus and neonate.

There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, SOTACOR should be used in pregnancy only if the potential benefits outweigh the possible risk to the foetus. The neonate should be monitored very carefully for 48 - 72 hours after delivery if it was not possible to interrupt maternal therapy with SOTACOR 2-3 days before the birthdate.

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended during administration of these compounds.

4.7 Effects on ability to drive and use machines

There are no data available, but the occasional occurrence of side-effects such as dizziness and fatigue should be taken into account (see section as jper IMB standard 4.8 Undesirable effects).

4.8 Undesirable effects

Sotacor is well tolerated in the majority with the most frequent adverse effects arising from beta-blockade properties. Adverse effects are usually transient in nature and rarely necessitate interruption of, or withdrawal from treatment. If they do occur, they usually disappear when the dosage is reduced. The most significant adverse effects, however, are those due to proarrhythmia, including torsades de pointes (see section as per IMB standard Warnings and Precautions).

The following are adverse events considered related to therapy, occurring in 1% or more of patients treated with SOTACOR.

Cardiovascular: Bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure, presyncope.

Dermatologic: Rash.

Gastro-intestinal: Nausea/vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence.

Musculoskeletal: Cramps.

Nervous / psychiatric: Fatigue, dizziness, asthenia, light-headedness, headache, sleep disturbances, depression, paraesthesia, mood
changes, anxiety.

Urogenital: Sexual dysfunction.

Special Senses: Visual disturbances, taste abnormalities, hearing disturbances.

Body as a whole: Fever.

In trials of patients with cardiac arrhythmia, the most common adverse events leading to discontinuation of SOTACOR were fatigue 4%, bradycardia (<50 bpm) 3%, dyspnoea 3%, proarrhythmia 2%, asthenia 2% and 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

Intentional or accidental over dosage with SOTACOR has rarely resulted in death. Haemodialysis results in a large reduction of plasma levels of sotalol.
Symptoms and treatment of over dosage: The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia. In cases of massive intentional over dosage (2-16 g) of SOTACOR the following clinical findings were seen: hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia, torsades de pointes.
If over dosage occurs, therapy with SOTACOR should be discontinued and the patient observed closely. In addition, if required, the following therapeutic measures are suggested:

Bradycardia: Atropine (0.5 to 2 mg IV), another anticholinergic drug, a beta-adrenergic agonist (isoprenaline, 5 microgram per minute, up to 25 microgram, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

D, l-sotalol is a non-selective hydrophilic β-adrenergic receptor blocking agent, devoid of intrinsic sympathomimetic activity or membrane stabilizing activity.
SOTACOR 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.

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, SOTACOR produces a gradual but significant reduction in both systolic and diastolic blood pressures in hypertensive patients.

5.2 Pharmacokinetic properties

The bioavailability of oral sotalol is essentially complete (greater than 90%). After oral administration, peak levels are reached in 2.5 to 4 hours, and steady-state plasma levels are attained within 2-3 days. The absorption is reduced by approximately 20% when administered with a standard meal, in comparison to fasting conditions. Over the dosage range 40-640 mg/day SOTACOR displays dose proportionality with respect to plasma levels. Distribution occurs to a central (plasma) and a peripheral compartment, with an elimination half-life of 10-20 hours. Sotalol does not bind to plasma proteins and is not metabolised. There is very little inter-subject variability in plasma levels. Sotalol crosses the blood brain barrier poorly, with cerebrospinal fluid concentrations only 10% of those in plasma. The primary route of elimination is renal excretion. Approximately 80 to 90% of a dose is excreted unchanged in the urine, while the remainder is excreted in the faeces. Lower doses are necessary in conditions of renal impairment (see Dosage and Administration in patients with renal dysfunction). Age does not significantly alter the pharmacokinetics, although impaired renal function in geriatric patients can decrease the excretion rate, resulting in increased drug accumulation.

5.3 Preclinical safety data

No further particulars.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Maize starch
Magnesium stearate
Stearic acid
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date for this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Overlabelled cardboard carton containing blister strips. Pack size 30.

6.6 Special precautions for disposal and other handling

No special requirements.

7 Parallel Product Authorisation Holder

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 Parallel Product Authorisation Number

PPA 1151/66/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23rd May 2008

10 DATE OF REVISION OF THE TEXT

August 2009