IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PPA1328/020/002
Case No: 2034068

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

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

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

Betaloc 100 Milligram Tablets

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 **26/03/2007** until **20/12/2011**.

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

Betaloc Tablets 100mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg Metoprolol tartrate
Excipients: Lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Product imported from the UK:
White to off-white, circular, biconvex tablet, scored and engraved ‘A/ME’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of hypertension and angina pectoris. Cardiac arrhythmias, especially supraventricular tachyarrhythmias.
Adjunct to the treatment of hyperthyroidism.
Early intervention with Betaloc in acute myocardial infarction reduces infarct size and the incidence of ventricular fibrillation. Pain relief may also decrease the need for opiate analgesics.
Betaloc has been shown to reduce mortality when administered to patients with acute myocardial infarction.
Prophylaxis of migraine.

4.2 Posology and method of administration

The tablets should be taken on an empty stomach.
The dose must always be adjusted to the individual requirements of the patient. The following are guidelines:

Hypertension

The recommended maintenance dosage in patients with hypertension is 100mg-200mg daily, given as a single dose in the morning or in divided doses (morning and evening). Begin with 50mg twice daily or 100mg once daily. Dose increments should be at intervals thereafter according to individual patient responses. Maximum dose, usually 200mg daily. Doses up to 400mg daily have been used. If needed,

other antihypertensive agents may be added.
Long-term antihypertensive treatment with metoprolol in daily doses of 100-200mg has been shown to reduce total mortality, including sudden cardiovascular death, stroke, and coronary events in hypertensive patients.

Angina Pectoris

The recommended dosage is 100-200mg daily, given in divided doses (morning and evening). Begin with 50mg twice daily. Dose increments should be at intervals thereafter according to individual patient responses.
Maximum dose, usually 200mg daily (in divided doses). Doses up to 300mg daily (in divided doses) have been used. If needed, other antianginal agents may be added.

Cardiac Arrhythmias

The recommended dosage is 100-200mg daily given in divided doses (morning and evening). If needed, other antiarrhythmic agents may be added.

Hyperthyroidism

The recommended dosage is 50mg four times a day.

Myocardial Infarction

Early intervention

To achieve optimal benefits from intravenous Betaloc suitable patients should present within 12 hours of the onset of chest pain. Therapy should commence with 5mg i.v. every 2 minutes to a maximum of 15mg total as determined by blood pressure and heart rate. The second or third dose should not be given if the systolic blood pressure is <90mmHg, the heart rate is <40 beats/min and the P-Q time is >0.26 seconds, or if there is any aggravation of dyspnoea or cold sweating. Oral therapy should commence 15 minutes after the last injection with 50mg every 6 hours for 48 hours. Patients who fail to tolerate the full intravenous dose should be given half the suggested oral dose.

Maintenance

The usual maintenance dose is 200mg daily, given in divided doses.

Migraine Prophylaxis

The recommended dosage is 100-200mg daily, given in divided doses (morning and evening).

Impaired Renal Function

Dose adjustment is generally not needed in patients with impaired renal function.

Impaired Hepatic Function

Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has a low protein binding (5-10%). However, a reduction in dosage may be necessary, according to

the severity of hepatic impairment.

Elderly

Several studies indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol.

Children

There is limited experience with metoprolol treatment in children.

4.3 Contraindications

Betaloc, as with other beta-blockers, should not be used in patients with any of the following:
- AV block of second- or third-degree,
- Unstable decompensated cardiac failure (pulmonary oedema, hypoperfusion or hypotension),
- Continuous or intermittent inotropic therapy acting through beta-receptor agonism,
- Bradycardia, (<45bpm),
- Sick sinus syndrome,
- Cardiogenic shock,
- Severe peripheral arterial circulatory disorder,
- Untreated phaeochromocytoma,
- Metabolic acidosis.

Known hypersensitivity to any component of Betaloc or other beta-blockers.
Betaloc is also contra-indicated when suspected acute myocardial infarction is complicated by bradycardia (<45bpm), first degree heart block (the P-Q interval is >0.24 sec) or systolic blood pressure <100mmHg.

4.4 Special warnings and precautions for use

Betaloc as with other beta-blockers:

• should not be withdrawn abruptly. When possible, Betaloc should be withdrawn gradually over a period of 10-14 days, in diminishing doses to 25mg daily for the last 6 days. During its withdrawal patients should be kept under close surveillance, especially those with known ischaemic heart disease. The risk for coronary events, including sudden death, may increase during the withdrawal of beta-blockade.

• must be reported to the anaesthetist prior to general anaesthesia. It is not generally recommended to stop Betaloc treatment in patients undergoing surgery.

• although contra-indicated in severe peripheral arterial circulatory disturbances (see Section 4.3), may also aggravate less severe peripheral arterial circulatory disorders.

• may be administered when heart failure has been controlled. Digitalisation and/or diuretic therapy should also be considered for patients with a history of heart failure, or patients known to have a poor cardiac reserve.

• may cause patients to develop increasing bradycardia, in such cases the Betaloc dosage should be reduced or gradually withdrawn.

• due to the negative effect on conduction time, may aggravate pre-existing conduction time disorders of moderate degree, which may lead to AV block, and should only be given with caution to patients with first degree heart block.

• may increase the number and duration of angina attacks in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Betaloc is a $beta_1$-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.

• may mask the early signs of acute hypoglycaemia, in particular tachycardia. During treatment with Betaloc, the risk of interfering with carbohydrate metabolism or masking hypoglycaemia is less than with non-selective beta-blockers.

• may mask the symptoms of thyrotoxicosis.

• may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

Although cardioselective beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all beta-blockers, these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use. When administration is necessary, these patients should be kept under close surveillance. The use of a $beta_2$-bronchodilator (e.g. terbutaline) may be advisable in some patients. The dosage of the $beta_2$-agonist may require an increase when treatment with Betaloc is commenced.

As with all beta-blockers, careful consideration should be given to patients with psoriasis before Betaloc is administered.

In the presence of liver cirrhosis the bioavailability of Betaloc may be increased.
In patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.
In labile and insulin-dependent diabetes it may be necessary to adjust the hypoglycaemic therapy.

Intravenous administration of calcium antagonists of the verapamil-type should not be given to patients treated with beta-blockers.
The initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

4.5 Interaction with other medicinal products and other forms of interaction

Betaloc can reduce myocardial contractility and impair intracardiac conduction. Care should be exercised when drugs with similar activity, e.g. antiarrhythmic agents (of the quinidine type and amiodarone), or general anaesthetics, are given concurrently.

Increased negative inotropic and chronotropic effects may occur when Betaloc is given together with calcium antagonists of the verapamil and diltiazem type, causing bradycardia, hypotension and asystole. In patients treated with beta-blockers intravenous administration of calcium antagonists of the verapamil-type should not be given in combination.

Patients receiving concomitant treatment with sympathetic ganglion blocking agents, other beta-blockers (i.e. eye drops), or Mono Amine Oxidase (MAO) inhibitors should be kept under close surveillance.

If concomitant treatment with clonidine is to be discontinued, Betaloc should be withdrawn several days before clonidine.

Betaloc will antagonise the $beta_1$-effects of sympathomimetic agents but should have little influence on the bronchodilator effects of $beta_2$-agonists at normal therapeutic doses.
The administration of adrenaline (epinephrine) to patients undergoing beta-blockade can result in an increase in blood pressure and bradycardia although this is less likely to occur with $beta_1$-selective drugs.

Betaloc may impair the elimination of lidocaine.

Metoprolol is a metabolic substrate for the Cytochrome P450 isoenzyme CYP2D6. Drugs that act as enzyme-inducing and enzyme-inhibiting substances may exert an influence on the plasma level of metoprolol. Plasma levels of metoprolol may be raised by co-administration of compounds metabolised by CYP2D6, e.g. antiarrhythmics, antihistamines, histamine-2-receptor antagonists, antidepressants, antipsychotics, and COX-2-inhibitors. The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

As with other beta-blockers, concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant treatment with indometacin or other prostaglandin synthetase inhibiting drugs may decrease the antihypertensive effect of beta-blockers.

The beta-blocker may mask some of the symptoms of thyrotoxicosis and of hypoglycaemia by inhibition of sympathetic nerve functions. The effects of hypoglycaemic agents may be increased, particularly by the non-cardioselective beta-blockers. The dosages of oral antidiabetics and also of insulin may have to be readjusted in patients receiving beta-blockers. The tachycardia of hypoglycaemia may be modified.

As beta-blockers may affect the peripheral circulation, care should be exercised when drugs with similar activity e.g. ergotamine are given concurrently.

The effects of Betaloc and other antihypertensive drugs on blood pressure are usually additive.

Care should be taken when combining with other antihypertensive drugs or drugs that might reduce blood pressure, such as tricyclic antidepressants, barbiturates and phenothiazines. However, combinations of antihypertensive drugs may often be used with benefits to improve control of hypertension.

4.6 Pregnancy and lactation

Pregnancy

Betaloc should not be used in pregnancy or nursing mothers unless the physician considers that the benefit outweighs the possible hazard to the foetus/infant. Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries.

As with all beta-blockers, Betaloc may cause side-effects especially bradycardia and hypoglycaemia in the foetus, and in the newborn and breastfed infant.
Betaloc has, however, been used in pregnancy associated hypertension under close supervision, after 20 weeks gestation. Although Betaloc crosses the placental barrier and is present in the cord blood, as yet no evidence of foetal abnormalities has been reported.

Lactation

The amount of metoprolol ingested via breast milk should not produce significant beta-blocking effects in the neonate if the mother is treated with the normal therapeutic doses.

4.7 Effects on ability to drive and use machines

Patients should know how they react to Betaloc before they drive or use machines because occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Betaloc is well tolerated and adverse reactions have generally been mild and reversible. The following events have been reported as adverse events in clinical trials or reported from routine use. A relationship to treatment with metoprolol has not always been established.
The following definitions of frequencies are used:
Very common (≥10%), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0.09%) and very rare (<0.01%).

Cardiovascular system

Common:	Bradycardia, postural disorders (very rarely with syncope), cold hands and feet, palpitations.
Uncommon:	Deterioration of heart failure symptoms, first-degree heart block, oedema, pericordial pain.
Rare:	Disturbances of cardiac conduction, cardiac arrhythmias.
Very rare:	Gangrene in patients with pre-existing severe peripheral circulatory disorders.

Central nervous system

Very common:	Fatigue.
Common:	Dizziness, headache.
Uncommon:	Paraesthesiae, muscle cramps.

Gastrointestinal

Common:	Nausea, abdominal pain, diarrhoea, constipation.
Uncommon:	Vomiting.
Rare:	Dry mouth.

Haematologic

Very rare:	Thrombocytopenia.

Hepatic

Rare:	Liver function test abnormalities.
Very rare:	Hepatitis.

Metabolism

Uncommon:	Weight gain.

Musculoskeletal

Very rare:	Arthralgia.

Psychiatric

Uncommon:	Depression, concentration impairment, somnolence or insomnia, nightmares.
Rare:	Nervousness, anxiety, impotence/sexual dysfunction.
Very rare:	Amnesia/memory impairment, confusion, hallucinations.

Respiratory

Common:	Dyspnoea on exertion.
Uncommon:	Bronchospasm.
Rare:	Rhinitis.

Sense organs

Rare:	Disturbances of vision, dry and/or irritated eyes, conjunctivitis.
Very rare:	Tinnitus, taste disturbances.

Skin

Uncommon:	Rash (in the form of urticaria psoriasiform and dystrophic

	skin lesions), increased sweating.
Rare:	Loss of hair.
Very rare:	Photosensitivity reactions, aggravated psoriasis.

4.9 Overdose

Symptoms

Poisoning due to an overdose of Betaloc may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness, coma, nausea, vomiting, cyanosis, hypoglycaemia and, occasionally, hyperkalaemia.

Concomitant ingestion of alcohol, antihypertensives, quinidine or barbiturates may aggravate the patient's condition.

The first manifestations usually appear 20 minutes to 2 hours after drug ingestion.

Management

Treatment should include close monitoring of cardiovascular, respiratory and renal function, and blood glucose and electrolytes. Further absorption may be prevented by induction of vomiting, gastric lavage or administration of activated charcoal if ingestion is recent. Cardiovascular complications should be treated symptomatically. In the presence of severe hypotension, bradycardia, and impending heart failure, administer a $beta_1$-agonist until the desired effect is achieved. Where a selective $beta_1$-agonist is not available, dopamine may be used; or atropine sulphate iv may be used in order to block the vagus nerve. If a satisfactory effect is not achieved, other sympathomimetic agents (e.g. noradrenaline [norepinephrine], metaraminol), or inotropic agents (e.g. dobutamine) may be used. Temporary pacing may be required for AV block. Glucagon can reverse the effects of excessive beta-blockade, given in a dose of 1-10mg intravenously.

Intravenous $beta_2$-stimulants e.g. terbutaline may be required to relieve bronchospasm.

It should be noted that the dosages of drugs (antidotes) needed to treat overdose of beta-blockade are much higher than normally recommended therapeutic dosages. This is because the beta-receptors are occupied by the beta-blocker.

The use of haemodialysis or haemoperfusion may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metoprolol is a competitive β-adrenoceptor antagonist. It acts preferentially to inhibit β_1-adrenoceptors (conferring some cardioselectivity), is devoid of intrinsic sympathomimetic activity (partial agonist activity) and possesses β-adrenoceptor blocking activity comparable in potency with propranolol.

A negative chronotropic effect on the heart is a consistent feature of metoprolol administration. Thus, cardiac output and systolic blood pressure rapidly decrease following acute administration.

5.2 Pharmacokinetic properties

Metoprolol tablets dissolve rapidly which results in a rapid and complete absorption with t_{max} within 2 hours and consistent bioavailability data between different study populations.
Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme.
Elimination is mainly via hepatic metabolism (>90%). Terminal half life is about 3-4 hours.

5.3 Preclinical safety data

The acute toxicity of metoprolol is low to moderate. Signs of toxicity are non-specific and do not indicate any target organ. Signs in rats and dogs indicate that metoprolol can exert a cardiopressive action at high plasma concentrations. Acute toxicity after oral administration is lower in rodents than in dogs.

There is no specific general toxicity after repeated administration to rats or dogs. Reproduction and mutagenicity studies have revealed no evidence of adverse effects. Carcinogenicity studies in rats and mice have shown no increased incidence of neoplasms related to metoprolol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycollate
Colloidal anhydrous silica
Povidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of 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.

6.5 Nature and contents of container

PVC/Aluminium blister packs:
100 (10 x 10 Blisters)

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

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8 Parallel Product Authorisation Number

PPA 1328/20/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 21st December 2006

10 DATE OF REVISION OF THE TEXT

February 2007