IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0073/098/001
Case No: 2036135

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

Antigen Pharmaceuticals Ltd

Roscrea, **Co. Tipperary**, **Ireland**

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

Metoprolol Tartrate Tablets 50mg

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 **25/04/2007** until **14/12/2007**.

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

Metoprolol Tartrate Tablets 50 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of metoprolol tartrate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet
Round, white tablet, embossed with ‘a’ on one face and with ‘M/50’ on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metoprolol tartrate tablets USP 50mg are indicated in the management of hypertension, angina pectoris and cardiac arrhythmias, especially supraventricular tachyarrhythmias, and as an adjunct to the treatment of thyrotoxicosis. They are also for use in the reduction of mortality following acute myocardial infarction. Metoprolol may be used for the prophylactic treatment of migraine.

4.2 Posology and method of administration

Metoprolol tartrate tablets 50mg are for oral administration.

Adults:

Hypertension
The initial dose is usually 100mg daily and, if required, this may be increased by weekly increments of 100mg per day up to a total daily dose of 400mg, given as a single dose or as a divided dose twice daily. Diuretics and other anti-hypertensive agents may be used concurrently if required.

Angina Pectoris
50mg - 100mg twice or three times daily.

Cardiac Arrhythmias
50mg twice or three times daily is usually adequate. This may be increased if necessary up to 100mg three times daily.

Thyrotoxicosis
50mg four times daily.

Prophylaxis following acute myocardial infarction
Oral therapy should commence 15 minutes after the last metoprolol injection and the oral dose is 50mg every six hours for forty eight hours. Thereafter, the maintenance dose is 100mg twice daily.

Migraine prophylaxis
100 to 200mg daily in two divided doses.

Children:

Not recommended, as the safety and efficacy of metoprolol in children have not been established.

4.3 Contraindications

1) 2nd or 3rd degree atrioventricular block.

2) Severe bradycardia.

3) Uncontrolled or digitalis/diuretic-refractory heart failure.

4) Cardiogenic shock.

5) Use in patients with severe asthma.

4.4 Special warnings and precautions for use

Sudden withdrawal of beta-adrenoceptor blocking agents in patients with ischaemic heart disease may result in the appearance of anginal attacks of increased frequency or severity or in deterioration in cardiac state. Discontinuation of therapy should be gradual.

In the event that a patient receiving a beta blocker requires anaesthesia, the anaesthetist should be informed of the use of medication prior to the use of a general anaesthetic to permit his taking the necessary precautions.

Metoprolol should only be used with caution in patients with controlled congestive cardiac failure. Evidence of recrudescence of this condition should be regarded as a signal to discontinue therapy.

Metoprolol may 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 beta-blocker, depending on the degree of airways resistance and the benefit derived from beta-blockade.

Beta blockers 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 noncardioselective beta blockers. The tachycardia of hypoglycaemia may be modified.

The initial treatment of severe hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of auto-regulatory mechanisms.

When this agent is administered to patients in renal failure, the interval between doses may need to be increased or the dosage reduced to avoid accumulation of the drug.

Some cases of ocular changes (conjunctivitis and 'dry eye') and/or skin rashes (including a psoriasiform type) have been reported in association with the use of beta-adrenoceptor blockers. Until their significance is known it is recommended that consideration be given to discontinuing such therapy if these effects appear.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Metoprolol should only be used with great caution in patients who are receiving concomitant myocardial depressants, a Class I antidysrhythmic agent such as disopyramide, procainamide or lignocaine, or a sympathomimetic such as adrenaline or noradrenaline (which reverse the hypotensive effects of the beta blocker and enhance its vasoconstrictor

activity).

Adrenergic neurone blocking agents such as guanethidine, rauwolfia alkaloids such as reserpine, and other antihypertensive agents including diuretics and the vasodilator group will have an additive effect on the hypotensive action of metoprolol.

If a beta blocker is used concurrently with clonidine, the clonidine should not be discontinued until several days after withdrawal of the beta blocker.

4.6 Pregnancy and lactation

Metoprolol has been given in pregnancy-associated hypertension after 20 weeks gestation. Although the drug crosses the placental barrier and is present in cord blood, there is no evidence up to the present time of foetal abnormalities. None the less the possibility cannot be excluded and the drug should only be used if considered essential and with the patient under close supervision. The drug is excreted in breast milk. This should be kept in mind if it is intended for use in nursing mothers.

4.7 Effects on ability to drive and use machines

Such abilities are generally unaffected during therapy with metoprolol.

4.8 Undesirable effects

Some cases of ocular changes (conjunctivitis and 'dry eye') and/or skin rashes (including a psoriasiform type) have been reported in association with the use of beta blockers (see 'Special Precautions for Use').

Central and peripheral nervous system:
Occasionally: fatigue, dizziness, headache.
Rarely: paraesthesiae, muscle cramp, depression, decreased mental alertness, somnolence or insomnia, nightmares.
In isolated cases: personality disorders, hallucinations.

4.9 Overdose

Overdosage may lead to pronounced bradycardia and hypotension. Following recent overdosage, the stomach should be emptied by gastric lavage and aspiration. Severe hypotension and bradycardia may respond to atropine sulphate 0.25 - 2.0 mg intravenously. If a satisfactory response is not achieved, a bolus dose of glucagon 5 - 10 mg may be administered, followed if necessary by an intravenous infusion of glucagon 1 - 5 mg per hour or more according to response and reducing the rate of infusion as the patient improves. Dobutamine has also been used to manage hypotension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Metoprolol is a relatively cardioselective beta-adrenoceptor blocking agent.

5.2 Pharmacokinetic properties

Following oral administration, metoprolol is readily absorbed and is subjected to significant first-pass metabolism in the liver, only one of the metabolites having some activity. Metoprolol crosses the placenta and is excreted in breast milk. Metoprolol has a half-life of 3 to 4 hours but it has a longer duration of biological activity.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Talc
Colloidal anhydrous silica
Magnesium stearate
Sodium starch glycollate Type A

6.2 Incompatibilities

None.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Polypropylene securitainers with tamper evident polypropylene caps.
Pack sizes: 100 and 500 tablets.

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

None.

7 MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd.
Roscrea
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 73/98/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 December 1987

Date of last renewal: 15 December 2002

10 DATE OF REVISION OF THE TEXT

April 2007