For the use only of a Registered Medical Practioner or a Hospital xxxxxxxx-5253

NEBICARD 5 MG TABLETS

(Nebivolol Hydrochloride Tablets)

COMPOSITION

NEBICARD-5 MG TABLETS : Each uncoated tablet contains:

Nebivolol hydrochloride

equivalent to Nebivolol..... 5 mg

PRODUCT DESCRIPTION

White to off-white, round, biconvex, uncoated tablets, with cross break line on one side and plain on other side.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Nebivolol is a lipophilic β1-blocker administered clinically as a racemic mixture of equal proportions of its d and l enantiomers. It is a competitive and highly selective beta-1 receptor antagonist with mild vasodilating properties, possibly due to an interaction with the L-arginine/nitric oxide pathway. Nebivolol has a protective effect on left ventricular function. The drug appears to reduce preload and maintain or decrease afterload. Heart rate and left ventricular end-diastolic pressure are decreased, whereas stroke volume is increased and cardiac output is maintained.

PHARMACOKINETICS

Absorption

After oral administration of Nebivolol tablet, the blood-drug concentration reaches peak value within 0.5 to 2 hrs and food has no effect on it. The oral bioavailability averages 12% in fast metabolisers and 96 % in slow metabolisers. At steady state and at the same dose level, the peak plasma concentration of unchanged nebivolol is about 23 times higher in poor metabolisers than in extensive metabolisers.

Distribution

In plasma, both nebivolol enantiomers are predominantly bound to albumin. Plasma protein binding is 98.1% for SRRR-nebivolol and 97.9% for RSSS-nebivolol.

Metabolism

Nebivolol is extensively metabolized, partly to active hydroxy-metabolites. Nebivolol is metabolized via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation; in addition, glucuronides of the hydroxy-metabolites are formed. The metabolism of nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism. When unchanged drug plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variation in rates of metabolism, the dose of Nebivolol should always be adjusted to the individual requirements of the patient: poor metabolisers therefore may require lower doses.

Steady-state plasma levels in most subjects (fast metabolisers) are reached within 24 hours for nebivolol and within a few days for the hydroxy-metabolites. Plasma concentrations are dose-proportional between 1 and 30mg. The pharmacokinetics of nebivolol is not affected by age.

Elimination

In fast metabolisers, elimination half-lives of the nebivolol enantiomers average 10 hours. In slow metabolisers, they are 3-5 times longer. In fast metabolisers, plasma levels of the RSSS-enantiomer are slightly higher than for the SRRR-enantiomer. In slow metabolisers, this difference is larger. In fast metabolisers, elimination half-lives of the hydroxy metabolites of both enantiomers average 24 hours, and are about twice as long as slow metabolisers.

INDICATIONS AND USAGE

NEBICARD is indicated in the treatment of essential hypertension.

CONTRAINDICATIONS

Nebivolol is contraindicated in the following conditions:

- Patients having Hypersensitivity to Nebivolol
- Liver insufficiency or liver function impairment
- Pregnancy and lactation
- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome, including sino-atrial block
- Second and third degree heart block
- History of bronchospasm and bronchial asthma
- untreated pheochromocytoma
- Metabolic acidosis
- Bradycardia (heart rate <50bpm)
- Hypotension
- Severe peripheral circulatory disturbances

WARNINGS AND PRECAUTIONS

Warnings:

In general, the following warnings and precautions apply to beta-adrenergic antagonists.

Anaesthesia: Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation. If beta blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand.

Cardiovascular: In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised.

In patients with ischaemic heart disease, treatment with a beta-adrenergic antagonist should be discontinued gradually, i.e. over 1-2 weeks. If necessary replacement therapy should be initiated at the same time, to prevent exacerbation of angina pectoris.

Beta-adrenergic antagonists may induce bradycardia: if the pulse rate drops below 50-55 bpm at rest and/or the patient experiences symptoms that are suggestive of bradycardia, the dosage should be reduced.

Precautions:

Beta-adrenergic antagonists should be used with caution:

- in patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur;
- in patients with first degree heart block, because of the negative effect of beta-blockers on conduction time;
- in patients with Prinzmetal's angina due to unopposed alphareceptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of anginal attacks.

Metabolic/Endocrinological: Care should be taken in diabetic patients, as Nebicard may mask certain symptoms of hypoglycaemia (tachycardia, palpitations).

Beta-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism.

Respiratory: In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated.

Other: Patients with a history of psoriasis should take beta-adrenergic antagonists only after careful consideration.

Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.

Use in pregnancy

Insufficient data exist on the use of Nebivolol in human pregnancy to determine its potential harmfulness. Animal studies have not shown any indication of harmful effects, other than on the basis of its pharmacological properties.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death and in immature and premature delivery. In addition, adverse effects (hypoglycemia and bradycardia) may occur in the foetus and the neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, Nebivolol should not be used during pregnancy.

Use in lactation

Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Since it is not known whether nebivolol is excreted into human milk, the use of Nebivolol when breast feeding is contra-indicated. Animal studies have shown that nebivolol is excreted in breast milk.

ADVERSE EVENTS

Most adverse events are mild to moderate. The most frequent adverse events (incidence between 1-10%) are headache, dizziness, tiredness and paresthesia. Other adverse events reported by at least 1% of the patients are diarrhoea, constipation, nausea, dyspnea and oedema.

Adverse events typical of beta-adrenergic antagonists, reported in less than 1% of the patients treated with Nebivolol are: bradycardia, slowed AV-conduction/AV-block, hypotension, heart failure, (increase of) intermittent claudication, impaired vision, impotence, depression, nightmares, dyspepsia, flatulence, vomiting, bronchospasm, rash.

The following adverse events have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud's phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.

DRUG INTERACTIONS

Calcium antagonists: Care should be exercised when administering beta-adrenergic antagonists with calcium antagonists of the verapamil or diltiazem type, because of their negative effect on contractility and atrio-ventricular conduction. Intravenous verapamil is contra-indicated in patients on Nebivolol.

Anti-arrhythmics: Caution should be exercised when administering beta-adrenergic antagonists in association with Class I anti-arrhythmic drugs and amiodarone, as their effect on atrial conduction time and their negative inotropic effect may be potentiated.

Clonidine: Beta-adrenergic antagonists increase the risk of rebound hypertension after sudden withdrawal of chronic clonidine treatment.

Digitalis: Digitalis glycosides associated with beta-adrenergic antagonists may increase atrio-ventricular conduction time. Clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

Insulin and oral anti-diabetic drugs: Although Nebivolol does not affect glucose levels, certain symptoms of hypoglycaemia (palpitations, tachycardia) may be masked.

Anaesthetics: Concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. The anesthetist should be informed when the patient is receiving Nebivolol.

Other: Concomitant use of NSAIDs had no effect on the blood pressure lowering effect of Nebivolol.

Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect. Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided Nebivolol is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.

Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. Co-administration of alcohol, furosemide or hydrocholorothiazide did not affect the pharmacokinetics of nebivolol.

Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.

Sympathomimetic agents may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathomimetic agents with both alpha- and beta-adrenergic effects (risk of hypertension, severe bradycardia and heart block).

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines may increase the blood pressure lowering effect.

As Nebivolol metabolism involves the CYP2D6 isoenzyme, concomitant administration of serotonin re-uptake inhibitor or other compounds predominantly metabolized via this pathway, may make extensive metabolisers resemble poor metabolisers.

DOSAGE AND ADMINISTRATION

The dose is one tablet daily, preferably at the same time of the day. Tablets may be taken with meals.

Patients with renal insufficiency: In patients with renal insufficiency, the recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg.

Patients with hepatic insufficiency: Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore the use of Nebicard in these patients is contraindicated.

Elderly: In patients over 65 years, the recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Children: No studies have been conducted in children. Therefore, use in children is not recommended.

Mode of Administration: Oral

OVER DOSAGE

Symptoms: Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Treatment: In case of overdosage, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any drug residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines.

The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5μg/minute, or dobutamine, starting with a dose of 2.5μg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50-100μg/kg i.v. may be considered. If required, the injection should be repeated within one hour, to be followed, if required by an i.v. infusion of glucagon 70μg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

STORAGE

Store below 30^{o}C, protected from moisture.

EXPIRY DATE

36 months from Manufacturing.

DATE OF PREPARATION

26 August 2014

PRESENTATION

NEBICARD-5 mg tablets are packed in Alu-Alu blister of 10 tablets. Such blisters containing 10 tablets are packed into a carton of 10's, 30's and 100's.

Not all presentations may be available locally.

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Manufactured by:
TORRENT PHARMACEUTICALS LTD.
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