Bystolic pharmaceutical particulars

Name of the medicinal product:
Nebivolol Tablets.

2. Qualitative and quantitative composition

Each Nebivolol 5mg Tablet contains 5mg of nebivolol (as hydrochloride)

Excipients: Lactose monohydrate

For a full list of excipients, see Section 6.1.

3. Pharmaceutical form

Tablets.

White, round, biconvex, 9mm diameter tablet, cross-scored on one side and marked with “N5” on the other side.

The tablet can be divided into equal quarters.

4. Clinical particulars
4.1 Therapeutic indications

Hypertension

Treatment of essential hypertension.

Chronic heart failure (CHF)

Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients 70 years old or above.

4.2 Posology and method of administration

Hypertension

Adults

The usual dose is one tablet (5mg) daily, preferably taken at the same time of the day. Tablets may be taken with meals.

The blood pressure lowering effect may take up to 1-2 weeks of treatment to become evident. Occasionally, the optimal effect is only reached only after 4 weeks.

Beta-blockers can be used alone or concomitantly with other antihypertensive agents. An additional antihypertensive effect has been observed when Nebivolol 5mg Tablets are combined with hydrochlorothiazide 12.5mg-25mg.

Patients with renal insufficiency

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

Patients with hepatic insufficiency

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

Elderly

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

Children and adolescents

Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy.

Chronic Heart Failure (CHF)

The use of nebivolol for treatment of stable chronic heart failure should involve a gradual increase of dosage until the optimal individual maintenance dose is reached.

Prior to starting treatment, patients should have stable chronic heart failure without acute failure during the past six weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

For those patients receiving cardiovascular drug therapy including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, these drugs should be maintained at a stable dose for the two weeks leading up to initiation of nebivolol treatment.

The dose should be increased from the initial dose of 1.25mg daily to 2.5mg and then to 5mg daily and then 10mg daily at intervals of 1-2 weeks based on patient tolerability.

The maximum recommended dose is 10mg nebivolol once daily.

The initiation of therapy and all increases in dose should be carried out under the supervision of an experienced physician over a period of at least 2 hours to ensure that the clinical status (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening heart failure) remains stable.

The occurrence of adverse events may prevent patients being treated with the maximum recommended dose. If necessary, the dose reached can also be decreased step by step and reintroduced as appropriate.

During the initial dose increasing phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of nebivolol, or to stop it immediately if necessary (in case of sever hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block).

Treatment of stable chronic heart failure with nebivolol is generally a long-term treatment.

The treatment with nebivolol is not recommended to be stopped abruptly since this might led to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be decreased step-wise weekly.

Patients with renal insufficiency

No dose adjustment is required in mild to moderate renal insufficiency since up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine ? 250µmol/L). Therefore, the use of nebivolol in these patients is not recommended.

Patients with hepatic insufficiency

Data in patients with hepatic insufficiency are limited. Therefore, the use of nebivolol in these patients is contraindicated.

Elderly

No dose adjustment is required since up-titration to the maximum tolerated dose is individually adjusted.

Children and adolescents

Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients.

• Liver insufficiency or liver function impairment.

• Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring I.V. inotropic therapy.

In addition, as with other beta-blocking agents, nebivolol is contra-indicated in:

• Sick sinus syndrome, including sino-atrial block.

• Second and third degree heart block (without a pacemaker).

• History of bronchospasm and bronchial asthma.

• Untreated phaeochromocytoma

• Metabolic acidosis.

• Bradycardia (heart rate < 60bpm prior to start of therapy)

• Hypotension (systolic blood pressure <90mmHg)

• Severe peripheral circulatory disturbances.

4.4 Special warnings and precautions for use

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.

Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

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 suggestive of bradycardia, the dosage should be reduced.

Beta-adrenergic antagonists should be used with caution in the following conditions:

• Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur upon use of beta blockers.

• First degree heart block, because of the negative effect of beta-blockers on conduction time

• Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Beta-adrenergic antagonists may increase the number and duration of anginal attacks.

• Concomitant treatment with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs. For details please refer to section 4.5.

Metabolic/Endocrinological

Nebivolol 5mg Tablets does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations).

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

Respiratory

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

Other

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

Caution should be exercised when treating patients with a history of psoriasis with beta-adrenergic antagonists as they may increase the sensitivity to allergens and the severity of anaphylactic reactions.

The initiation of Chronic Heart Failure treatment with nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:

Combinations not recommended:

• Class I anti-arrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone) as the effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased (see section 4.4).

• Calcium channel antagonists of verapamil/diltiazem the type due to a negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with ?-blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).

• Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine). Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation) (see section 4.4). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of hypertension.

Combinations to be used with caution:

• Class III anti-arrhythmic drugs (Amiodarone) as the effect on atrio-ventricular conduction time may be potentiated.

• Volatile halogenated anaesthetics as concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). Sudden withdrawal of beta-blocker treatment should be avoided if possible. The anaesthesiologist should be informed when the patient is receiving Nebivolol 5mg Tablets.

• Insulin and oral anti-diabetic drugs as, although nebivolol does not affect glucose levels, concomitant use may mask symptoms of hypoglycaemia (palpitations, tachycardia).

• Baclofen (antispastic agent), amifostine (antineoplastic adjunt): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medication should be adjusted accordingly.

Combinations to be used only after careful consideration:

• Digitalis glycosides as concomitant use may increase atrio-ventricular conduction time although clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

• Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine) because concomitant use may increase the risk of hypotension, and cause an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure.

• Antipsychotics and antidepressants (tricyclics, barbiturates and phenotiazines). Concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

• Non steroidal anti-inflammatory drugs (NSAID) are thought to have no effect on the blood pressure lowering effect of nebivolol.

• Sympathomimetic agents. Concomitant use 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 causing increased risk of hypertension, severe bradycardia and heart block.

Pharmacokinetic interactions:

As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine, quinidine and bupropion, chloroquine, levomepromazine, dextrometorphan and terbinafine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events.

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 hydrochlorothiazide did not affect the pharmacokinetics of nebivolol. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.