NEBİX (Nebivolol)

Film Coated Tablets

COMPOSITION
Nebix range is available for oral administration.

1. **Nebix 2.5mg tablets:** Each film coated tablet contains Nebivolol (as HCl) 2.5mg.
2. **Nebix 5mg tablets:** Each film coated tablet contains Nebivolol (as HCl) 5mg.
3. **Nebix 10mg tablets:** Each film coated tablet contains Nebivolol (as HCl) 10mg.

DESCRIPTION
NEBIX is a selective beta blocker agent.

PHARMACOLOGICAL PROPERTIES
Pharmcodynamics
Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol)It combines two pharmacological activities:
It is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRR-enatiomer (d-enantiomer).
It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.
Single and repeated doses of nebivolol reduce heart rate and blood pressure at rest and during exercise, both in normotensive subjects and in hypertensive patients. The antihypertensive effect is maintained during chronic treatment.
At therapeutic doses, nebivolol is devoid of alpha-adrenergic antagonism.
During acute and chronic treatment with nebivolol in hypertensive patients systemic vascular resistance is decreased. Despite heart rate reduction, reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamic differences as compared to other beta1 receptor antagonists has not been fully established.
In hypertensive patients, nebivolol increases the NO-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction
Pharmacokinetics
Nebivolol is a lipophilic, cardioselective beta-blocker without ISA or membrane stabilising properties (l-enantiomer). It also has a nitric oxide mediated vasodilatory effect (d-enantiomer).
Absorption: Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food; nebivolol can be given with or without meals.
Metabolism: Nebivolol is extensively metabolised, 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. The oral bioavailability of nebivolol averages 12% in fast metabolisers and is virtually complete 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. 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.
Furthermore, the dose should be adjusted for patients over 65 years, patients with renal insufficiency and patients with hepatic insufficiency. Steady-state plasma levels in most subjects are reached within 24 hours for nebivolol and within a few days for the hydroxy-metabolites.
Plasma concentrations are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol are not affected by age.
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.
The volume of distribution is between 10.1 and 39.4 l/kg.
Excretion: One week after administration, 38% of the dose is excreted in the urine and 48% in the faeces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.
Drug Interactions
NEBIX should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists, or antiarrhythmic agents, are used concurrently. Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.
NEBIX should not be combined with other β-blockers. In patients who are receiving NEBIX and clonidine, NEBIX should be discontinued for several days before the gradual tapering of clonidine.
CYP2D6 Inhibitors: Use caution when NEBIX is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.)

INDICATIONS
1. Hypertension
2. Chronic heart failure (CHF)
   a. Treatment of chronic heart failure in addition to standard therapies in elderly patients of 70 years or older.

DOSAGE AND ADMINISTRATION
Hypertension
Adults: The dose is one tablet (5 mg) daily, preferably at the same time of the day.
The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.
Combination with other antihypertensive agents: Beta-blockers can be used alone or concomitantly with other antihypertensive agents. To date, an additional antihypertensive effect has been observed only when Nebivolol 5 mg is combined with hydrochlorothiazide 12.5-25 mg.
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 Nebivolol in these patients is contra-indicated.
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 and adolescents: Nebivolol is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.
Chronic heart failure (CHF)
The treatment of stable chronic heart failure has to be initiated with a gradual uptitration of dosage until the optimal individual maintenance dose is reached.
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, dosing of these drugs should be stabilised during the past two weeks prior to initiation of Nebivolol treatment.
The initial uptitration should be done according to the following steps at 1-2 weekly intervals based on patient tolerability: 1.25 mg nebivolol, to be increased to 2.5 mg nebivolol once daily, then to 5 mg once daily and then to 10 mg once daily. The maximum recommended dose is 10 mg nebivolol once daily.
Initiation of therapy and every dose increase should be done 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 of heart failure) remains stable.
Occurrence of adverse events may prevent all 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 titration 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 severe 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 lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should be gradually decreased divided into halves weekly.
Special Populations
Patients with renal insufficiency: No dose adjustment is required in mild to moderate renal insufficiency since uptitration 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 contra-indicated.
Elderly: No dose adjustment is required since uptitration to the maximum tolerated dose is individually adjusted.
Children and adolescents: Nebivolol is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy

CONTRAINDICATIONS
NEBIX is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), or severe hepatic impairment (Child-Pugh >B), and in patients who are hypersensitive to any component of this product.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
The most common adverse events that led to discontinuation of NEBIX were headache (0.4%), nausea (0.2%) and bradycardia (0.2%). Other adverse events rarely seen are: Headache, Fatigue, Dizziness, Diarrhea, Nausea, Insomnia, Chest pain, Bradycardia, Dyspnea, Rash, Peripheral edema

Abrupt Cessation of Therapy
Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. As with other β-blockers, when discontinuation of NEBIX is planned, patients should be carefully observed and advised to minimize physical activity. NEBIX should be tapered over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, it is recommended that NEBIX be promptly reinstituted, at least temporarily.
Cardiac Failure: In patients who have compensated congestive heart failure, NEBIX should be administered cautiously. If heart failure worsens, discontinuation of NEBIX should be considered.
Angina and Acute Myocardial Infarction:NEBIX was not studied in patients with angina pectoris or who had a recent MI.
Bronchospastic Diseases: In general, patients with bronchospastic diseases should not receive β-blockers.
Anesthesia and Major Surgery: If NEBIX is to be continued perioperatively, patients should be closely monitored when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used.
Diabetes and Hypoglycemia: β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. It is not known whether nebivolol has these effects. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be advised about these possibilities and nebivolol should be used with caution.
Thyrotoxicosis: β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.
Peripheral Vascular Disease: β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in these patients.
Non-dihydropyridine Calcium Channel Blockers: Because of significant negative inotropic and chronotropic effects in patients treated with - β blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be used in patients treated concomitantly with these agents and ECG and blood pressure should be monitored.

Risk of Anaphylactic Reactions
While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.
In patients with known or suspected pheochromocytoma, an alpha-blocker should be initiated prior to the use of any β-blocker.

PREGNANCY & LACTATION
Pregnancy Category C: No studies of nebivolol were conducted in pregnant women. NEBIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: NEBIX is not recommended during nursing.

OVERDOSE
The most common signs and symptoms associated with NEBIX overdosage are bradycardia and hypotension. Other important adverse events reported with NEBIX overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse events associated with β-blocker overdose include bronchospasm and heart block.
Due to extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.
If overdose occurs, NEBIX should be stopped and general supportive and specific symptomatic treatment should be provided.

STORAGE
Store below 25°C in a dry place. Protect from light.

PRESENTATION
1. **Nebix 2.5mg film coated tablets:** Blister Pack of 1x14 tablets.
2. **Nebix 5mg film coated tablets:** Blister Pack of 1x14 tablets.
3. **Nebix 10mg film coated tablets:** Blister Pack of 1x14 tablets.

TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

نیبکس

(نیبی ولول)

فلم کوٹڈ گولیاں

50130209

خوراک

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