PRESCRIBING INFORMATION: For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

NEBTAS-H

(Nebivolol and Hydrochlorthiazide Tablets (5+12.5) mg)

COMPOSITION:

Each uncoated tablet contains:
Nebivolol Hcl eq. to Nebivolol..... 5 mg
Hydrochlorothiazide Ph.Eur..... 12.5 mg
Also contains Lactose

DESCRIPTION

Nebivolol

Nebivolol is the racemate (dl-nebivolol) of the enantiomers l-nebivolol and d-nebivolol. It is a competitive and highly selective beta-1 receptor antagonist.

Hydrochlorothiazide

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:

Clinical Pharmacology

Mechanism of Action:

The mechanism of action of the antihypertensive response of nebivolol has not definitively established. Possible factors that may be involved include: (1) decreased heart rate (2) decreased myocardial contractility, (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of rennin activity and (5) vasodilatation and decreased peripheral vascular resistance.

Pharmacokinetic properties

Concomitant administration of nebivolol and hydrochlorothiazide has no effect on the bioavailability of either active substance. The combination tablet is bioequivalent to the concomitant administration of the separate components.

Nebivolol

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.

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. 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 tablet should always be adjusted to the individual requirements of the patient: poor metabolisers therefore may require lower doses.

Plasma concentrations are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol is 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.

Bio-transformation

Nebivolol is extensively hydroxylated, partly to active Hydroxyl-metabolites. Nebivolol is hydroxyled via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation; in addition, glucuronides of the hydroxyl-metabolites are formed. The metabolism of nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism.

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 hydroxymetabolites of both enantiomers average 24 hours, and are about twice as long in slow metabolisers.

Steady-state plasma levels in most subjects (fast metabolisers) are reached within 24 hours for nebivolol and within a few days for the hydroxyl-metabolites.

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.

Hydrochlorothiazide

Absorption

Hydrochlorothiazide is well absorbed (65 to 75 %) following oral administration. Plasma concentrations are linearly related to the administered dose. The absorption of Hydrochlorothiazide is dependent on intestinal transit time, being increased when the intestinal transit time is slow, for example when given with food. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours and peak plasma levels were observed within 1 and 5 h after dosing.

Distribution

Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 l/kg. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Biotransformation

Hydrochlorothiazide metabolism is very poor. Almost all of hydrochlorothiazide is excreted in the urine unchanged.

Elimination

Hydrochlorothiazide is eliminated primarily by the renal pathway. More than 95 % of hydrochlorothiazide appears unchanged in the urine within 3-6 hours after an oral dose. In patients with renal disease, plasma concentrations of Hydrochlorothiazide are increased and elimination half-life is prolonged.

Pharmacokinetic properties

Pharmacotherapeutic group: Beta blocking agents, selective, and thiazides

Nebivolol hydrochloride and hydrochlorothiazide tablet is a combination of nebivolol, a selective beta-receptor antagonist, and hydrochlorothiazide, a thiazide diuretic. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

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.

In vitro and in vivo experiments in animals showed that nebivolol has no intrinsic sympathicomimetic activity.

In vitro and in vivo experiments in animals showed that at pharmacological doses nebivolol has no membrane hydrolyzed action.

In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma hydrox activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

INDICATION

This combination is indicated for the treatment of hypertension.

DOSAGE AND ADMINISTRATION

Adults

Nebivolol hydrochloride and hydrochlorothiazide Tablets is indicated in patients whose blood pressure is demonstrated to be adequately controlled on nebivolol 5 mg and hydrochlorothiazide 12.5 mg given concurrently.

The dose is one tablet (5 mg/12.5 mg) daily, preferably at the same time of the day. Tablets may be taken with meals.

Patients with renal insufficiency

Nebivolol hydrochloride and hydrochlorothiazide Tablets should not be given to patients with severe renal insufficiency.

Patients with hepatic insufficiency

Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore the use of Nebivolol hydrochloride and hydrochlorothiazide Tablets in these patients is contra-indicated.

Elderly

In view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Children and adolescents

No studies have been conducted in children and adolescents. Therefore, use in children and adolescents is not recommended.

Route of administration: Oral

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Hypersensitivity to other sulphonamide-derived substances.
- Liver insufficiency or liver function impairment.
- Anuria, severe renal insufficiency (creatinine clearance < 30 ml/min.).
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring i.v. inotropic therapy.
- Sick sinus syndrome, including sino-atrial block.
- Second and third degree heart block (without a pacemaker).
- Bradycardia (heart rate < 60 bpm prior to start therapy).
- Hypotension (systolic blood pressure < 90 mmHg).
- Severe peripheral circulatory disturbances.
- History of bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia

WARNINGS AND PRECAUTIONS

All warnings related to each monocomponent, as listed below, should apply also to the fixed combination of Nebivolol hydrochloride and hydrochlorothiazide tablets.

Nebivolol

The following warnings and precautions apply to beta-adrenergic antagonists in general.

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 hydroxyled.

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.

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.

Combination of nebivolol with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Metabolic/Endocrinological: Nebivolol 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 intensify symptoms.

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.

Hydrochlorothiazide

Renal impairment: Full benefit from thiazide diuretics can be derived only if the kidney function is not altered. In patients with renal disease, thiazides may increase azotaemia. Cumulative effects of this active substance may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Metabolic and endocrine effects: Thiazide therapy may impair glucose tolerance. Dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients.

Electrolyte imbalance: As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH. Patients with long QT syndrome, either congenital or iatrogenic, are particularly at high risk in case of hypokalaemia. Hypokalaemia increases the cardiotoxicity of digitalis glycosides and the risk of cardiac arrhythmia. More frequent plasma potassium monitoring is indicated in patients at risk of hypokalaemia, starting within the week after initiation of therapy.

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment.

Thiazides may decrease urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. A marked hypercalcaemia may be the evidence of a hidden hyperparathyroidism. Thiazides should be discontinued before carrying out test for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lupus erythematosus: Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Anti-doping test: Hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

Other: Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Photosensitivity reactions have been reported with thiazide diuretics in rare cases. If photosensitivity reactions occur during treatment, it is recommended to stop the treatment. If a re-administration of treatment is deemed necessary, it is recommended to protect exposed areas from the sun or artificial UVA-light.

Protein bound iodine: Thiazides may decrease serum protein bound iodine levels without signs of thyroid disturbance.

Nebivolol/Hydrochlorothiazide Combination

In addition to the warnings related to the monocomponents, the followings specifically apply to Nebivolol hydrochloride and hydrochlorothiazide tablets:

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malapsorption should not take this medicinal product.

DRUG INTERACTIONS

Pharmacodynamic interactions:

Nebivolol

The following interactions apply to beta-adrenergic antagonists in general.

Combinations not recommended

Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with ß-blocker treatment may lead to profound hypotension and atrio-ventricular block.

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). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Class III antiarrhythmic drugs (Amiodarone): effect on atrio-ventricular conduction time may be potentiated.

Anaesthetics – volatile halogenated: concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension. As a general rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is receiving nebivolol hydrochloride and hydrochlorothiazide tablets.

Insulin and oral antidiabetic drugs: although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia).

Combinations to be taken in account

Digitalis glycosides: concomitant use 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.

Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

Non steroidal anti-inflammatory drugs (NSAID): no effect on the blood pressure lowering effect of nebivolol.

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

Hydrochlorothiazide

Potential interactions related to hydrochlorothiazide:

Concomitant use not recommended

Lithium: The renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased when used in concomitance with hydrochlorothiazide. Therefore the use of nebivlolol hydrochloride and hydrochlorothiazide tablets in combination with lithium is not recommended. If the use of such combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium levels: The potassium-depleting effect of hydrochlorothiazide may be potentiated by the coadministration of other medicinal products associated with potassium loss and hypokalaemia (eg other kaliuretic diuretics, laxatives, corticosteroids, ACTH, hydroxylted, carbenoxolone, penicillin G sodium or salicylic acid derivatives). Such concomitant use is therefore not recommended.

Concomitant use requiring caution

Non steroidal anti-inflammatory drugs (NSAID): NSAIDs (ie acetylsalicylic acid (> 3 g/day), COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of thiazide diuretics.

Calcium salts: Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when nebivolol hydrochloride and hydrochlorothiazide tablets is administered with medicinal products affected by serum potassium disturbances (eg digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine IV).

Non-depolarizing skeletal muscle relaxants (eg tubocurarine): The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Antidiabetic medicinal products (oral agents and insulin): The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicinal product may be required.

Metformin: Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and diazoxide: The hyperglycaemic effect of beta-blockers other than nebivolol and diazoxide may be enhanced by thiazides.

Pressor amines (eg noradrenaline): The effect of pressor amines may be decreased.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol): Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Thiazides may increase the risk of adverse effects caused by amantadine.

Salicylates: In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Cyclosporine: Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Iodinated contrast media: In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before the administration.

Potential interactions related to both Nebivolol and Hydrochlorothiazide:

Concomitant use to be taken into account

Other anti-hypertensive drugs: there may be additive hypotensive effects or potentiation during concomitant treatment with other anti-hypertensive drugs.

Antipsychotics, tricyclic antidepressants, barbiturates, narcotic drugs and alcohol: concomitant administration of Nebivolol hydrochloride and hydrochlorothiazide tablets with these medicines may enhance the hypotensive effect and/or lead to postural hypothension.

Pharmacokinetic interactions:

Nebivolol

As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine and quinidine 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 hydrochloride and hydrochlorothiazide tablets 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.

Hydrochlorothiazide

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins (e.g *cholestyramine and colestipol resins*).

Cytotoxic agents: With concurrent use of hydrochlorothiazide and cytotoxic agents (*eg cyclophosphamide, fluorouracil, methotrexate*) increased bone marrow toxicity (in particular granulocytopenia) has to be expected.

ADVERSE EFFECTS

Adverse events are listed separately for each single active substance.

Nebivolol

The adverse reactions reported following administration of nebivolol alone, which are in most of the cases of mild to moderate intensity, are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	Common (≥1/100 to < 1/10)	Uncommon (≥1/1,000 to 1/100)	Very Rare (≤1/10,000)	Not Known
Immune system disorders				Angioneurotic oedema, hypersensitivity
Psychiatric disorders		nightmares; depression		
Nervous system disorders	headache, dizziness, paraesthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/AV -block		
Vascular disorders		hypotension, (increase of) intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnoea	bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhoea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	psoriasis aggravated	
Reproductive system and breast disorders		impotence		
General disorders and administration site conditions	tiredness, oedema			

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

Hydrochlorothiazide

The adverse events that have been reported with the use of hydrochlorothiazide alone include the following:

Blood and lymphatic system disorders: hydroxylate, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow failure.

Immune system disorders: anaphylactic reaction.

Metabolism and nutritional disorders: anorexia, dehydration, gout, diabetes mellitus, metabolic alkalosis, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypomagnesaemia, hypochloraemia, hypercalcaemia), hyperglycaemia, hyperamylasaemia.

Psychiatric disorders: apathy, confusional state, depression, nervousness, restlessness, sleep disorder.

Nervous system disorders: convulsions, depressed level of consciousness, coma, headache, dizziness, paraesthesia, paresis.

Eye disorders: xanthopsia, blurred vision, myopia (aggravated), lacrimation decreased.

Ear and labyrinth disorders: vertigo.

Cardiac disorders: cardiac arrhythmias, palpitations.

Vascular disorders: orthostatic hypotension, thrombosis, embolism, shock

Respiratory, thoracic and mediastinal disorders: respiratory distress, pneumonitis, interstitial lung disease, pulmonary oedema.

Gastrointestinal disorders: dry mouth, nausea, vomiting, stomach discomfort, diarrhoea, constipation, abdominal pain, ileus paralytic, flatulence, sialoadenitis, pancreatitis.

Hepato-biliary disorders: jaundice cholestatic, cholecystitis.

Skin and subcutaneous tissue disorders: pruritus, purpura, urticaria, photosensitivity reaction, rash, cutaneous lupus erythematosus, vasculitis hydroxylated, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders: muscle spasms, myalgia.

Renal and urinary disorders: renal impairment, renal failure acute, nephritis interstitial, glycosuria.

Reproductive system and breast disorders: erectile dysfunction.

General disorders and administration site conditions: asthenia, pyrexia, fatigue, thirst.

Investigations: electrocardiogram change, blood cholesterol increased, blood triglycerides increased.

OVERDOSAGE

No data are available on overdosage with nebivolol. Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage with hydrochlorothiazide are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

STORAGE

Store below 30°C in dry & dark place.

PRESENTATION

NEBTAS-H tablets are available in blister of 10 tablets.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

Selaqui, Dehradun-248 197, INDIA