NEBICARD-H

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

Abbreviated Prescribing information for NEBICARD-H

(Nebivolol Hydrochloride and Hydrochlorothiazide Tablets) [Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

Mechanism of Action: Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS nebivolol (or l-nebivolol). It combines two pharmacological activities: 1) It is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRRenatiomer (d-enantiomer). 2) It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway. **Hydrochlorothiazide:** It blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. Metabolic toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

INDICATIONS: It is indicated for the treatment of Essential Hypertension.

DOSAGE AND ADMINISTRATION: Nebivolol 5 mg, Hydrochlorothiazide 12.5 mg. The recommended dosage is once daily or as directed by the Physician.

CONTRAINDICATION: ***Nebicard H*** is contraindicated in patients with hypersensitivity, active liver disease, Acute heart failure**,** Sick sinus syndrome**,** History of bronchospasm and bronchial asthma, Untreated phaeochromocytoma, metabolic acidosis, Bradycardia, Hypotention, severe peripheral circulatory disturbances, Anuria.

WARNINGS & PRECAUTIONS: ***Nebivolol:*** *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*: 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. *Metabolic/Endocrinological:* Nebivolol Hydrochloride 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) also may mask tachycardia 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. ***Hydrochlorothiazide*****:** *Acute Myopia and Secondary Angle-Closure Glaucoma* : Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. *Diabetes and Hypoglycemia:* Latent diabetes mellitus may become manifest and diabetic patients given thiazides may require adjustment of their insulin dose. *Renal Disease* : Cumulative effects of the thiazides may develop in patients with impaired renal function. In such patients, thiazides may precipitate azotemia. *Hyperuricemia* or acute gout may be precipitated in certain patients receiving thiazide diuretics. *Impaired Hepatic Function* : Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate hepatic coma in patients with severe liver disease. *Parathyroid Disease:* Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and

hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy. Non-melanoma skin cancer: An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC, *Choroidal Effusion:* can cause idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma.

DRUG INTERACTIONS: ***Nebivolol:*** *Pharmacodynamic interactions* Combinations not recommended *:* Class I antiarrhythmics, Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction, Centrally-acting antihypertensive(clonidine, guanfacin, moxonidine, methyldopa, rilmenidine). Combinations to be used with caution: Class III antiarrhythmic drugs (Amiodarone): effect on atrio-ventricular conduction time may be potentiated. Combinations to be used only after careful consideration : Digitalis glycosides, Calcium antagonists of the dihydropyridine type 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. Pharmacokinetic interactions : 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. Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect. ***Hydrochlorothiazide:*** When given concurrently the following drugs may interact with thiazide diuretics**:** 1) Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur**.** 2) Antidiabetic drugs (oral agents and insulin): dosage adjustment of the antidiabetic drug may be required. 3) Other antihypertensive drugs: additive effect or potentiation. 4) Cholestyramine and colestipol resins: Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. 5) Corticosteroid, ACTH: intensified electrolyte depletion, particularly hypokalemia. 6) Pressor amines (e.g., norepinephrine), Lithium, Non-steroidal anti-inflammatory drugs, Drug/Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: ***Nebivolol:***: hallucinations, psychoses, confusion, cold/cyanotic extremities, raynaud phenomenon, dry eyes, oculo-mucocutaneous toxicity of the practolol-type, headache, dizziness, paraesthesia**,** bradycardia, heart failure and slowed AV conduction AV-block. ***Hydrochlorothiazide:*** Hypotension including orthostatic hypotension, Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia, Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura, Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia, Muscle spasm, Vertigo, paresthesia, dizziness, headache, restlessness, Transient blurred vision, xanthopsia, non-melanoma skin cancer and Impotence, Choroidal Effusion.

MARKETED BY:

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(Additional information is available on request)