NEBICARD-V

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

Abbreviated Prescribing information for NEBICARD-V

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

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue product as soon as possible
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the
- Developing fetus.

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. **Valsartan:** Angiotensin II (Ang II), the principal pressor agent of the renin-angiotensin system is formed from angiotensin I (Ang I) in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). The actions of angiotensin II include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and ventricular hypertrophy, and renal reabsorption of sodium.

Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.

INDICATIONS: It is indicated for the treatment of Hypertension.

DOSAGE AND ADMINISTRATION: Nebivolol 5 mg & Valsartan 80 mg. The recommended dosage is once daily or as directed by the Physician.

CONTRAINDICATION: Nebicard V: Hypersensitivity to the active substance or to any of the excipients listed. Liver insufficiency or liver function impairment. Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring i.v. inotropic therapy. Valsartan is contraindicated in second and third trimester of pregnancy and Severe hepatic impairment, biliary cirrhosis and cholestasis. The concomitant use of valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m2). In addition, as with other beta-blocking agents, nebivolol is contraindicated 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 < 60 bpm prior to start therapy). Hypotension (systolic blood pressure < 90 mmHg). Severe peripheral circulatory disturbances.

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. ***Valsartan:*** Hyperkalaemia: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended, Impaired renal function: The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73m2), Hepatic impairment: In patients with mild to moderate hepatic impairment without cholestasis, Valsartan should be used with caution, Sodium and/or volume depleted patients: In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan, for example by reducing the diuretic dose, Renal artery stenosis: other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan, Kidney transplantation, Primary hyperaldosteronism, Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy, Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy, Recent myocardial infarction, Heart failure, History of angioedema, Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS) and Paediatric population: Impaired renal function and Impaired hepatic function

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. ***Valsartan:*** **Concomitant use not recommended:** *Lithium*- Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists including with valsartan. **Caution required with concomitant use:** Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs. **Others:** In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide. **Paediatric population:** In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored**.**

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 ***Valsatan:*** *Common***:** Dizziness, Low blood pressure with or without symptoms such as dizziness and fainting when

standing up, Decreased kidney function (signs of renal impairment). *Uncommon*: Angioedema , Sudden loss of consciousness (syncope), spinning sensation (vertigo), Severely decreased kidney function (signs of acute renal failure), Muscle spasms, abnormal heart rhythm (signs of hyperkalaemia), Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (signs of cardiac failure), Headache, cough, Abdominal pain, Nausea, Diarrhoea, Tiredness, Weakness. *Not known*: Blistering skin, allergic reactions, Purplish-red spots, fever, itching, Unusual bleeding or bruising, Muscle pain, Decrease of level of haemoglobin, Increase of level of potassium in the blood, Elevation of liver function values, Increase of level of blood urea nitrogen and increase of level of serum and Low level of sodium in the blood.

MARKETED BY:

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(Additional information is available on request)