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CURRENT APPROVED PROFESSIONAL INFORMATION AUGUST 2025

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NEBIMAK 5 (Tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEBIMAK 5: Each tablet contains nebivolol hydrochloride equivalent to nebivolol 5 mg.

Contains sugar: (141.84 mg of lactose monohydrate)

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

NEBIMAK 5: White to off white, circular, biconvex uncoated tablets, debossed with "T 56" on one side and cross score line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEBIMAK 5 Treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology

Adults:

Take one 5 mg tablet daily, preferable at the same time of the day, with or without meals.

Combination with other antihypertensive agents:

An additional antihypertensive effect has been observed only when **NEBIMAK 5** is combined with hydrochlorothiazide 12.5 - 25 mg.

Patients with renal insufficiency:

The recommended starting dose is 2.5 mg daily. The daily dose may be increased to 5 mg if needed.

Patients with hepatic insufficiency:

There is no data in patients with hepatic insufficiency or impaired liver function. Therefore the use of **NEBIMAK 5** is contraindicated in these patients.

Elderly:

In patients over 65 years, the recommended starting dose is 2.5 mg daily. The dose may be increased to 5 mg daily if needed. Due to limited experience inpatients above 75 years, caution must be exercised and these patients monitored closely

Method of administration

For oral use

4.3 Contraindications

NEBIMAK 5 is contraindicated in patients with known Hypersensitivity to nebivolol hydrochloride or any of the excipients of NEBIMAK 5, (listed in section 6.1).

- Liver insufficiency or liver function impairment

- Pregnancy and breastfeeding
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring i.v. inotropic therapy.
- Untreated phaeochromocytoma
- Metabolic acidosis
- Sick sinus syndrome, including sino-atrial block
- Bradycardia (heart rate < 50 bpm)
- 2nd and 3rd degree heart block
- Hypotension
- History of bronchospasm and bronchial asthma
- Severe peripheral circulatory disorders
- Verapamil therapy

Children, as safety and efficacy has not been demonstrated.

4.4 Special warnings and precautions for use

Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.

Cardiovascular: Beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure, unless their condition has been stabilized. One of the pharmacological actions of beta- blockers is to reduce the heart rate.

Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (over a period of 1-2 weeks) and patients should be advised to limit the extent of their physical activity during the period that their medicine may be discontinued. 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:

- Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication) as the disorders may be aggravated
- 1st 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-blockers may increase the number and duration of anginal attacks.

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.

Metabolic/Endocrinological: Symptoms of hypoglycaemia (tachycardia, palpitations) may be masked in diabetic patients. Tachycardic symptoms may be masked in hyperthyroidism. Abrupt withdrawal may intensify symptoms.

Respiratory: Bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.

Other: Psoriasis may be aggravated. Patients with phaeochromocytoma should not receive beta-blockers without concomitant alpha adrenoreceptor blocking therapy.
Beta-blockers may unmask myasthenia gravis.
Adverse reactions are more common in patients with renal decompensation, and in patients who receive beta-blockers intravenously.

Information about excipients

NEBIMAK 5 contains lactose. Patients with rare hereditary problems of galactose intolerance, total

lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicines and other forms of interaction

Calcium antagonists:

Caution should be exercised when administering beta-blockers with calcium antagonists of the verapamil or diltiazem type because of their negative effect on contractility and atrioventricular conduction. Exaggeration of these effects can occur particularly in patients with impaired ventricular function and/or sinoatrial (SA) or atrioventricular (AV)-conduction abnormalities. Neither medicine should therefore be administered intravenously within 48 hours of discontinuing the other.

Anti-dysrhythmics:

Caution should be exercised when administering beta-blockers with Class I anti-dysrhythmic drugs and amiodarone as their effect on atrial conduction time and their negative inotropic effect may be potentiated. Such interactions can have life threatening consequences.

Clonidine:

Beta-blockers increase the risk of rebound hypertension after sudden withdrawal of chronic clonidine treatment.

Digitalis:

Digitalis glycosides associated with beta-blockers may increase atrio-ventricular conduction times. Nebivolol does not influence the kinetics of digoxin and clinical trials have not shown any evidence of an interaction.

Special note: Digitalisation of patients receiving long term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. The combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages and of individual patient's response (notably pulse rate) is essential in this situation.

Insulin and oral antidiabetic medicines:

Glucose levels are unaffected, however symptoms of hypoglycaemia may be masked.

Anaesthetics:

Concomitant use of beta-blockers and anaesthetics e.g. ether, cyclopropane and trichloroethylene may attenuate reflex tachycardia and increase the risk of hypotension.

Baclofen (antispastic agent), amifostine (antineoplastic adjunct):

Concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medicines should be adjusted accordingly

Other:

Provided NEBIMAK 5 is taken with a meal and an antacid between meals, the two treatments can be co-prescribed.

Sympathicomimetic agents may counteract the effect of beta-blockers.

Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines may increase the blood pressure lowering effect.

Concomitant administration of serotonin re-uptake inhibitors or other compounds predominantly metabolised by the CYPZD6 pathway may delay oxidative metabolism of beta- blockers.

4.6 Fertility, pregnancy and lactation

Pregnancy

Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If

treatment with beta-adrenoceptor blockers is necessary, beta$_1$-selective adrenoceptor blockers are preferable.

Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored.

Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breast-feeding

Animal studies have shown that nebivolol is excreted in breast milk. It is not known whether this drug is excreted in human milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Therefore, breastfeeding is not recommended during administration of **NEBIMAK 5**.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that nebivolol does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

4.8 Undesirable effects

Tabulated summary of adverse events

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Not known	non-thrombocytopenic purpura, thrombocytopenia, agranulocytosis, transient eosinophilia,

System Organ Class	Frequency	Undesirable effects
Immune system disorders:	Not Known:	Angioneurotic oedema, hypersensitivity
Psychiatric disorders:	Less Frequent:	Nightmares; depression
	Not Known:	Hallucinations, psychoses, confusion, Sleep disturbances, overt psychosis
Nervous system disorders:	Frequent:	Headache, dizziness, paraesthesia
	Less Frequent:	Syncope
	Not Known:	Peripheral neuropathy, myopathies
Eye disorders:	Less Frequent:	Impaired vision
	Not Known:	Decreased tear production, blurred vision, soreness
Cardiac disorders:	Less Frequent:	Bradycardia, heart failure, slowed AV conduction/AV-block
	Not Known:	Heart failure

System Organ Class	Frequency	Undesirable effects
Vascular disorders:	Less Frequent:	Hypotension, (increase of) intermittent claudication
	Not Known:	Raynaud phenomenon, peripheral gangrene
Respiratory, thoracic and mediastinal disorders:	Frequent:	Dyspnoea
	Less Frequent:	Bronchospasm
	Not Known:	Pneumonitis, pleurisy
Gastrointestinal disorders:	Frequent:	Constipation, nausea, diarrhoea
	Less Frequent:	Dyspepsia, flatulence, vomiting
	Not Known:	Abdominal cramping, sclerosing peritonitis, retroperitoneal fibrosis
Metabolic and nutritional disorders:	Not Known:	Hypoglycaemia
Skin and subcutaneous tissue disorders:	Less Frequent:	Pruritus, rash erythematous, psoriasis aggravated
	Not Known:	Urticaria Mucocutaneous toxicity of the practolol-type, skin rash, reversible alopecia, lupus like syndrome
Reproductive system and breast disorders:	Less frequent:	Impotence
General disorders and	Frequent:	tiredness, oedema

System Organ Class	Frequency	Undesirable effects
administration site conditions:	Not known:	Cold/cyanotic extremities

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

4.9 Overdose

Symptoms:

Bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Treatment:

Blood glucose levels should be checked and symptomatic and supportive therapy given.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 7.1.3 - Other hypotensives

Pharmacotherapeutic group: Beta blocking agent, selective,

ATC code: C07AB12.

5.1 Pharmacodynamic properties

Pharmacodynamics:

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 Bi-receptor antagonist which is attributable to the d-enantiomer

- It has mild vasodilating properties, possible due to an interaction with the L-arginine/nitricoxide pathway.

Nebivolol reduces heart rate and blood pressure at rest and during exercise. In healthy volunteers it has no significant effect on maximal exercise or endurance.

An in vitro and in vivo experiment in animals showed that nebivolol has no intrinsic sympathicomimetic activity and at pharmacological doses has no membrane stabilising effect. It is also devoid of a-adrenergic antagonism at therapeutic doses.

5.2 Pharmacokinetic properties

Nebivolol can be given with or without meals with peak plasma concentrations occuring within 2 to 6 hours after dosing. It is extensively metabolised partly to active hydroxy metabolites. The bioavailability of nebivolol averages 12 % in extensive metabolisers (EM's) and is virtually complete in poor metabolisers (PM's), but the mean bioavailability of the separate enantiomers and hydroxylated metabolites was fairly similar between EM's and PM's and no differences were found in the pharmacodynamic effects.

Steady-state plasma levels for nebivolol are reached within 24 hours in most subjects (EM's). The elimination half-lives of the hydroxy-metabolites of both enantiomers average 24 hours in EM's and are twice as long in PM's. Plasma concentrations are dose proportional and the pharmacokinetics of nebivolol are unaffected by age.

Nebivolol is highly protein bound; d-nebivolol being 98,1 % and l-nebivolol 97,9 % bound to albumin. About 52 % of the dose is excreted in urine and about 15 % in the faeces in PM's one week after administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content: Corn starch / Maize starch, croscarmellose sodium, hydroxypropyl methyl cellulose, polysorbate 80, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate

Contains sugar: Lactose monohydrate (141.84 mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the manufacturing date for blister pack.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Blister pack:

Tablets are packed in a blister containing plain aluminium foil with heat seal lacquered as the lidding material and clear PVC/PVDC as the forming material. The blister is packed in an outer carton.

Blister pack cold form:

Tablets are packed in a blister containing plain aluminium foil with heat seal lacquered as the lidding material and cold form laminate as the forming material. The blister is packed in an outer carton.

Pack sizes include 10, 28 or 30 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

56/7.1.3/0393

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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