Professional information for NEBILET 5 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NEBILET 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg nebivolol (as nebivolol hydrochloride).

Excipients with known effects:

Contains sugar: 141,75 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

An off-white, circular, biconvex tablet with one-sided dividing cross score. The tablet can be divided in equal quarters.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Treatment of mild to moderate essential hypertension.

Chronic heart failure (CHF)

Treatment of stable mild and moderate chronic heart failure in addition to standard therapies in

elderly patients ≥ 70 years.

4.2 Posology and method of administration

Posology

Hypertension

Adults:

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

The blood pressure-lowering effect usually 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 such as NEBILET 5 mg can be used alone or concomitantly with other antihypertensive medicines.

An additional antihypertensive effect has been observed only when NEBILET 5 mg 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 NEBILET 5 mg is contraindicated in these patients.

Elderly patients:

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 in patients above 75 years, caution must be exercised, and these patients monitored closely.

Paediatric population:

NEBILET 5 mg should not be used in children and adolescents as the safety and efficacy has not been established.

Chronic heart failure (CHF)

The treatment of stable chronic heart failure must be initiated with a gradual up-titration 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 doctor should be experienced in the management of chronic heart failure.

For those patients receiving cardiovascular medicines including diuretics and/or digoxin and/or ACE inhibitors and/or angiotensin II antagonists, dosing of these medicines should be stabilised during the previous two weeks prior to initiation of NEBILET 5 mg treatment.

The initial up-titration should be done according to the following steps at intervals of 1 – 2 weeks based on patient tolerability:

1,25 mg nebivolol, to be increased to 2,5 mg 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 doctor over a period of at least 2 hours to ensure that the clinical status (especially the 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 NEBILET 5 mg, 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 NEBILET 5 mg is generally a long-term treatment. The treatment with NEBILET 5 mg 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 by halving it weekly.

Patients with renal insufficiency:

No dose adjustment is required in mild to moderate renal insufficiency since up-titration to the maximum tolerated dose is individually adjusted. There is no experience in patients with severe renal insufficiency (serum creatinine ≥ 250 µmol/L). Therefore, the use of NEBILET 5 mg in these patients is not recommended.

Patients with hepatic insufficiency:

Data in patients with hepatic insufficiency are limited. Therefore, the use of NEBILET 5 mg in these patients is contraindicated.

Elderly patients:

No dose adjustment is required since up-titration to the maximum tolerated dose is individually adjusted.

Paediatric population:

NEBILET 5 mg should not be used in children and adolescents.

Method of administration

Oral administration.

Tablets may be taken with or without meals.

4.3 Contraindications

- Hypersensitivity to nebivolol or to any of the excipients listed in section 6.1.

- Liver insufficiency or liver function impairment.
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring IV inotropic therapy.
- Pregnancy and lactation.
- Cardiogenic shock.
- Uncontrolled heart failure.
- Sick sinus syndrome, including sino-atrial block.
- 2nd and 3rd degree heart block (without a pacemaker).
- History of bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Bradycardia (heart rate < 60 bpm prior to start of therapy).
- Hypotension (systolic blood pressure < 90 mm Hg).
- Severe peripheral circulatory disorders.
- In combination with verapamil therapy.

4.4 Special warnings and precautions for use

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

Anaesthesia

Continuation of beta-blockade reduces the risk of dysrhythmias during induction and intubation. If beta-blockade is interrupted in preparation for surgery, NEBILET 5 mg 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

Beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure,

unless their condition has been stabilised.

In patients with ischaemic heart disease, treatment with a beta-adrenergic antagonist, including NEBILET 5 mg, should be discontinued gradually, over a period of 1 – 2 weeks. If necessary, replacement therapy should be initiated at the same time, to prevent exacerbation of angina pectoris.

Beta-adrenergic antagonists, including NEBILET 5 mg, 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, including NEBILET 5 mg, should be used with caution in patients with:

- 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, such as NEBILET 5 mg, on conduction time.
- Prinzmetal angina due to unopposed alpha receptor-mediated coronary artery vasoconstriction. Beta-blockers such as NEBILET 5 mg may increase the number and duration of anginal attacks.

Combination of NEBILET 5 mg with calcium channel antagonists of the verapamil and diltiazem type, with Class I antidysrhythmic medicines, and with centrally acting antihypertensive medicines is not recommended (see sections 4.3 and 4.5).

Metabolic/Endocrinological

NEBILET 5 mg does not affect the glucose levels in diabetic patients. Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations). NEBILET 5 mg may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may intensify symptoms.

Respiratory

In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists including NEBILET 5 mg should be used with caution as airway constriction may be aggravated.

Other

Patients with a history of psoriasis should take NEBILET 5 mg only after careful consideration.
NEBILET 5 mg may increase the sensitivity to allergens and the severity of anaphylactic reactions.
The initiation of chronic heart failure treatment with NEBILET 5 mg necessitates regular monitoring. For the posology and method of administration please refer to section 4.2. Treatment discontinuation should not be done abruptly unless clearly indicated (see section 4.2).
Patients with phaeochromocytoma should not receive NEBILET 5 mg without concomitant alpha-adrenoreceptor blocking therapy.
Beta-blockers such as NEBILET 5 mg may unmask myasthenia gravis.

Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta-blockers, such as NEBILET 5 mg are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect.

If a beta-blocker, such as NEBILET 5 mg and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur.

Lactose monohydrate

NEBILET 5 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take NEBILET 5 mg.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

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

Combinations not recommended

Class I antidysrhythmic medicines (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased (see section 4.4).

Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with beta-blocker treatment, such as NEBILET 5 mg may lead to profound hypotension and atrio-ventricular block (see section 4.3).

Centrally acting antihypertensive medicines (clonidine, guanfacine, moxonidine, methyldopa, rilmenidine): concomitant use of centrally acting antihypertensive medicines may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation) (see section 4.4). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation such as NEBILET 5 mg, may increase risk of rebound hypertension.

Combinations to be used with caution

Class III antidysrhythmic medicine (amiodarone): effect on atrio-ventricular conduction time may be potentiated. Such interactions can have life-threatening consequences.

Anaesthetics – volatile halogenated: concomitant use of beta-adrenergic antagonists such as NEBILET 5 mg and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). As a rule, avoid sudden withdrawal of beta-blocker treatment. The anaesthesiologist should be informed when the patient is taking NEBILET 5 mg.

Insulin and oral antidiabetic medicines: although NEBILET 5 mg does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia).

Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensive medicine is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medicine should be adjusted accordingly.

Combinations to be considered

Digoxin: 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).

Nonsteroidal anti-inflammatory drugs (NSAIDs): no effect on the blood pressure-lowering effect of nebivolol, as in NEBILET 5 mg.

Sympathicomimetic agents: concomitant use may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic antagonists 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).

Pharmacokinetic interactions

As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially serotonin re-uptake inhibitors (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 NEBILET 5 mg is taken with the meal, and an antacid between meals, the two medicines can be co-prescribed.

Combining nebivolol with nicardipine slightly increased the plasma levels of both medicines, 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.

4.6 Fertility, pregnancy and lactation

NEBILET 5 mg is contraindicated in pregnancy and lactation.

Pregnancy

Nebivolol, as in NEBILET 5 mg, has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, beta-adrenoceptor blockers including NEBILET 5 mg reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects such as hypoglycaemia and bradycardia may occur in the fetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, $beta_1$-selective adrenoceptor blockers are preferable.

If treatment with nebivolol as in NEBILET 5 mg is considered necessary, the uteroplacental blood flow and the fetal growth should be monitored. In case of harmful effects on pregnancy or the fetus

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.

Breastfeeding

Mothers on NEBILET 5 mg should not breastfeed.

Fertility

The effect of nebivolol as in NEBILET 5 mg on human fertility is unknown.

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 NEBILET 5 mg does not affect psychomotor function. NEBILET 5 mg may cause side effects, such as dizziness and fatigue and can affect the ability to drive a vehicle and use machines (see section 4.8).

4.8 Undesirable effects

Adverse events are listed separately for hypertension and congestive heart failure (CHF) because of differences in the background diseases.

Hypertension

The adverse reactions reported, 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

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to ≤ 1/100)**	**Very rare (≤ 1/10 000)**	**Not known**
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, erythematous rash	aggravated psoriasis	urticaria

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to ≤ 1/100)**	**Very rare (≤ 1/10 000)**	**Not known**
Reproductive system and breast disorders		impotence		
General disorders and administration site conditions	tiredness, oedema			

The following side effects have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud's phenomenon, dry eyes and oculo-mucocutaneous toxicity, sleep disturbances and abdominal cramping.

Chronic heart failure (CHF)

Data on adverse reactions in CHF patients are available from one placebo-controlled clinical trial involving 1 067 patients taking nebivolol and 1 061 patients taking placebo. In this study, a total of 449 nebivolol patients (42,1 %) reported at least possibly causally related adverse reactions compared to 334 placebo patients (31,5 %). The most commonly reported adverse reactions in nebivolol patients were bradycardia and dizziness, both occurring in approximately 11 % of patients.

The following incidences were reported for adverse reactions (at least possibly medicine-related) which are considered specifically relevant in the treatment of chronic heart failure:

- Aggravation of cardiac failure occurred in 5,8 % of nebivolol patients compared to 5,2 % of placebo patients.
- Postural hypotension was reported in 2,1 % of nebivolol patients compared to 1,0 % of placebo patients.

- Medicine intolerance occurred in 1,6 % of nebivolol patients compared to 0,8 % of placebo patients.
- First degree atrio-ventricular block occurred in 1,4 % of nebivolol patients compared to 0,9 % of placebo patients.
- Oedema of the lower limb were reported by 1,0 % of nebivolol patients compared to 0,2 % of placebo patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NEBILET 5 mg 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 the South African Health Products Regulatory Authority (SAHPRA) via the 6.04 Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No data available on overdosage with NEBILET 5 mg.

Symptoms

Symptoms of overdosage with beta-blockers such as NEBILET 5 mg are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Treatment

In case of overdosage or hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Absorption of any medicine residues still present in the gastrointestinal tract can be prevented by the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. The

beta-blocking effect of NEBILET 5 mg can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2,5 µg/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50 – 100 µg/kg IV may be considered. If required, the injection should be repeated within one hour, to be followed if required by an IV infusion of glucagon 70 µg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives.

Pharmacotherapeutic group: Beta blocking agent, selective.

ATC code: C07AB12.

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 which is attributable to the d-enantiomer.
- It has mild vasodilating properties, possibly 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 $beta_1$ 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 a mortality–morbidity, placebo-controlled trial performed in 2 128 patients ≥ 70 years (median age 75,2 years) with stable chronic heart failure with or without impaired left ventricular ejection fraction (LVEF) (mean LVEF: 36 ± 12,3 %, with the following distribution: LVEF less than 35 % in 56 % of patients, LVEF between 35 % and 45 % in 25 % of patients and LVEF greater than 45 % in 19 % of patients) followed for a mean time of 20 months, nebivolol, on top of standard therapy, significantly prolonged the time to occurrence of deaths or hospitalisations for cardiovascular reasons (primary end-point for efficacy) with a relative risk reduction of 14 % (absolute reduction: 4,2 %). This risk reduction developed after 6 months of treatment and was maintained for all treatment duration (median duration: 18 months). The effect of nebivolol was independent from age, gender, or left ventricular ejection fraction of the population on study. The benefit on all-cause mortality did not reach statistical significance in comparison to placebo (absolute reduction: 2,3 %). A decrease in sudden death was observed in nebivolol treated patients (4,1 % vs 6,6 %, relative reduction of 38 %).

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.

In healthy volunteers it has no significant effect on maximal exercise or endurance.

Available preclinical and clinical evidence in hypertensive patients has not shown that nebivolol has a detrimental effect on erectile function.

5.2 Pharmacokinetic properties

Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food, it can be given with or without meals with peak plasma concentrations occurring within 2 to 6 hours after dosing. It is extensively metabolised partly to active hydroxy metabolites.

Nebivolol is metabolised 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. When unchanged nebivolol 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 NEBILET 5 mg should always be adjusted to the individual requirements of the patient. Poor metabolisers therefore may require lower doses.

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 hydroxy metabolites 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 hydroxy metabolites. Plasma concentrations are dose proportional between 1 mg and 30 mg. The pharmacokinetics of nebivolol are unaffected by age.

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.

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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity, reproductive and developmental toxicity and carcinogenic potential. Adverse effects

on the reproductive function were only recorded at high doses, exceeding by several fold the maximum recommended human dose (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium (E468)

Hypromellose (E464)

Lactose monohydrate

Magnesium stearate (E572)

Maize starch

Microcrystalline cellulose (E460)

Polysorbate 80 (E433)

Silica, colloidal anhydrous (E551).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Tablets are packed in PVC/aluminium blister strips, in an outer cardboard carton in pack sizes of 28 or 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Menarini South Africa (Pty) Ltd

Waterside Place, Unit 02D, South Gate Office Park

Carl Cronje Drive, Tygervalley

Cape Town 7530

Tel: +27 21 109 6444

8. REGISTRATION NUMBER

34/7.1.3/0495

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 August 2001

10. DATE OF REVISION OF THE TEXT

18 April 2024