Professional Information for NOMOWAKE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

NOMOWAKE 25 film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 25 mg doxylamine succinate.

Contains 50 mg mannitol (sugar alcohol) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

Blue, oval, biconvex, coated and scored tablet.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOMOWAKE is indicated for the alleviation of insomnia.

4.2 Posology and method of administration

Posology:

Adults (over 12 years old)

One to two tablets with water at bedtime.

This product should be used occasionally and should not be used successively for periods exceeding several days. If insomnia persists consult your doctor.

Paediatric population

NOMOWAKE should not be used in children under 12 years.

Method of administration:

Orally.

4.3 Contraindications

- Hypersensitivity to doxylamine succinate, or to any of the excipients listed in section 6.1.
- Hypersensitivity to other antihistamines.
- Pregnancy and lactation (see section 4.6).
- Epileptics.
- Patients with severe cardiovascular disorders.
- Acute asthma attack.
- Concomitant use of monoamine oxidase inhibitors (MAOIs) (see section 4.5).

4.4 Special warnings and precautions for use

The treatment period should be as short as possible. Treatment usually lasts from a few days to a week. NOMOWAKE should not be taken for more than 7 days unless advised by the medical practitioner.

Concomitant use of other CNS depressant medicines:

Alcohol intake should be avoided during treatment with NOMOWAKE (see section 4.5).

Hepatic and/or renal impairment:

Caution is advised in patients with hepatic and/or renal impairment. The dose should be reduced to 12,5 mg per day.

Cardiovascular disorders:

NOMOWAKE should be used with caution in patients with QT prolongation. Even though extension of this interval has not been observed with doxylamine succinate, other antihistamines may produce an extension of this interval. NOMOWAKE is contraindicated in severe cardiovascular disorders (see section 4.3).

Epilepsy:

NOMOWAKE is contraindicated in patients with epilepsy (see section 4.3).
Antihistamines sometimes produce hyperexcitability, even at therapeutic doses, which could decrease the seizure threshold.

Hearing:

Antihistamines may mask ototoxic effects of some medicines such as parenteral aminoglycosides, carboplatin, cisplatin, chloroquine and erythromycin. Periodical auditory function assessment is recommended with concomitant use of NOMOWAKE.

Dehydration:

NOMOWAKE could aggravate the symptoms of dehydration and heat stroke due to decreased sweating caused by anticholinergic effects.

Elderly patients:

Caution is advised in elderly patients (over 65 years of age) because of the increased susceptibility to side effects. The effectiveness of treatment should be continuously assessed.
Higher risk of falls has been reported in elderly patients (see section 4.8).

Daytime sleepiness:

If daytime sleepiness occurs, it is recommended to reduce the dose or NOMOWAKE should be taken earlier to ensure a minimum interval of 8 hours until awakening.

Other conditions that require caution:

NOMOWAKE should be used with caution in patients with the following conditions:

- Chronic bronchitis and emphysema.
- Angle closure glaucoma
- Prostate hyperplasia.
- Pyloroduodenal obstruction.
- Duodenal stenosis.
- Bladder neck obstruction.
- Hypokalaemia or other electrolyte abnormalities.

4.5 Interaction with other medicines and other forms of interaction

NOMOWAKE may enhance the sedative effects of central nervous system (CNS) depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics.

Epinephrine (adrenaline) should not be used to treat hypotension in patients taking NOMOWAKE, because the administration of epinephrine can cause a greater drop in blood pressure. Norepinephrine can be used to treat severe states of shock (see section 4.9).

Some antihistamines can prolong the QT interval. The concomitant use of NOMOWAKE with medicines (antidysrhythmic medicines, certain antibiotics, certain medicines for malaria, certain antihistamines, certain anti-hyperlipidaemic medicines or certain neuroleptic medicines) that prolong the QT interval should be avoided, although this effect has not been observed with

doxylamine succinate.

Antihypertensive medicines with an effect on the central nervous system (CNS), such as clonidine, may intensify the sedative effect of NOMOWAKE when taken concomitantly.

NOMOWAKE has additive antimuscarinic action with other antimuscarinic medicines, such as some antidepressants and monoamine oxidase inhibitors (MAOIs) (see section 4.3)

Interactions with food:

Food does not affect the bioavailability of NOMOWAKE.

Interactions with diagnostic tests:

NOMOWAKE may interfere with skin allergy tests that use allergens. NOMOWAKE should be discontinued at least three days before allergy tests.

Impact of other medicines on the pharmacokinetics of doxylamine:

Enzymes responsible for metabolising doxylamine succinate are not known. Therefore, strong CYP450 inhibitors should not be used concurrently with doxylamine succinate, given the increased exposure to these medicines, and therefore the increased risk of adverse events and sedation during the day.

These include selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine), macrolide antibiotics (clarithromycin, erythromycin, telithromycin), antidysrhythmic medicines (amiodarone), antiviral protease inhibitors (indinavir, ritonavir), and compounds with antifungal azoles (fluconazole, ketoconazole, itraconazole, voriconazole), terbinafine and bupropion.

Effects of doxylamine on the pharmacokinetics of other medicines:

Knowledge of the potential of doxylamine to inhibit the metabolism of other medicines is limited. Therefore, medicines with a narrow therapeutic index should not be used in combination with

NOMOWAKE given the risk of increased exposure to these medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy:

It is known that doxylamine succinate crosses the placenta. NOMOWAKE should not be used during pregnancy (see section 4.3).

Breastfeeding:

NOMOWAKE should not be used during breastfeeding (see section 4.3).

Fertility:

There are no fertility data available.

4.7 Effects on ability to drive and use machines

NOMOWAKE may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of treatment with NOMOWAKE, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

4.8 Undesirable effects

Summary of the safety profile:

Adverse reactions are generally mild and transient, being more frequent in the first days of treatment. The most common adverse reactions are drowsiness and anticholinergic effects, such as dry mouth, constipation, blurred vision, urinary retention, increased bronchial secretion and dizziness.

Tabulated list of adverse reactions:

Blood and lymphatic system disorders:

Less frequent: Haemolytic anaemia, thrombocytopenia, leucopenia, agranulocytosis.

Psychiatric disorders:

Frequent: Insomnia, nervousness.

Less frequent: Nightmares, agitation, euphoria, depression.

Nervous system disorders:

Frequent: Drowsiness, dizziness, headache.

Less frequent: Tremor, seizures.

Eye disorders:

Frequent: Blurred vision.

Less frequent: Diplopia.

Ear and labyrinth disorders:

Frequent: Vertigo.

Less frequent: Tinnitus.

Cardiac disorders:

Less frequent: Tachycardia.

Vascular disorders:

Less frequent: Orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Increased bronchial secretions.

Less frequent: Dyspnoea, chest tightness.

Gastrointestinal disorders:

Frequent: Dry mouth, constipation, pain in the upper abdomen.

Less frequent: Nausea, vomiting, diarrhoea, dyspepsia, anorexia, increased appetite.

Skin and subcutaneous tissue disorders:

Less frequent: Rash.

Renal and urinary disorders:

Frequent: Urinary retention.

Less frequent: Difficulty in micturition, dysuria.

General disorders and administration site conditions:

Frequent: Fatigue.

Less frequent: Asthenia, peripheral oedema, feeling of relaxation.

Frequency unknown: Malaise.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of NOMOWAKE is important. It allows continued monitoring of the benefit/risk balance of NOMOWAKE. 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

NOMOWAKE overdose should be considered a multiple intoxication, i.e. by ingestion of various medicines.

The most common symptom is impaired consciousness. Other symptoms include psychotic behaviour, antimuscarinic symptoms such as tachycardia and mydriasis, cardiovascular collapse, respiratory depression, seizures, loss of consciousness, coma and death. A serious complication can be rhabdomyolysis, with subsequent renal failure. Therefore, it is justified by a systematic review to determine the creatine kinase activity (CPK).

Since there is no specific antidote for overdose with an antihistamine, such as NOMOWAKE, treatment is symptomatic and supportive.
NOMOWAKE elimination is usually complete within 24 – 48 hours.

Using haemodialysis, peritoneal dialysis and haemofiltration in the context of an overdose with NOMOWAKE has not been studied. Forced diuresis is effective only to a limited extent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.2 Sedative, hypnotics.

Pharmacotherapeutic group: Aminoalkyl ethers.

ATC code: R06AA09.

Mechanism of action:

Doxylamine is an antihistamine ethanolamine derivative with reversible competitive, and the nonspecific histamine H_1 receptor antagonist activity.

Pharmacodynamics effects:

Doxylamine has sedative and hypnotic actions, as well as antiemetic and anticholinergic activity. Doxylamine can cross the blood-brain barrier acting on H_1 receptors to produce sedation. The sedative effect may also be produced by serotonergic antagonism and muscarinic receptors. The sleep-inducing effect is reached within 30 minutes with a maximum effect reached between 1 – 3

hours after administration. The duration is 6 – 8 hours.

Clinical efficacy and safety:

Doxylamine is effective in reducing the time to sleep onset as well as to increase the depth and duration.

5.2 Pharmacokinetic properties

Absorption:

Doxylamine shows high solubility and *in vitro* data (Caco-2 cells) suggest a high permeability. Maximum absorption following oral administration is reached within 2 – 3 hours (T_{max}).

Distribution:

General distribution occurs quickly. Its binding to plasma proteins is low compared with other antihistamines, with values of human albumin binding of 24 %. Doxylamine can cross the brain barrier.

Biotransformation:

Doxylamine is metabolised in the liver. Doxylamine is transformed into its demethylated metabolites and *N*-acetylated.

Elimination:

Plasma half-life is about 13 hours. It is mainly excreted in the urine.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol (E421)

Microcrystalline cellulose

Sodium carboxymethyl starch

Colloidal anhydrous silica (E551)

Magnesium stearate (E572)

Coating:

Indigo carmine aluminium lake (E132), containing:

Indigo carmine

Hydrated aluminium oxide

Opadry Y-1-7000, consisting of:

Hypromellose (E464)

Titanium dioxide (E171)

Polyethylene glycol (macrogol 400) (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Packed in aluminium/aluminium blister strips.

Pack sizes: 14 or 28 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal are required.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Ground Floor, Unit 6

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

54/2.2/0168

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 November 2022

10. DATE OF REVISION OF THE TEXT