ZADA PHARMACEUTICALS

Summary of Product Characteristics

1. Name of the medicinal product

NITRAX 40 mg tablets, prolonged release
NITRAX 60 mg tablets, prolonged release

2. Qualitative and quantitative composition

Each tablet contains 40 mg or 60 mg of isosorbide 5-mononitrate (ISMN).
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets (prolonged release).

4. Clinical particulars

4.1 Therapeutic indications

NITRAX is indicated in adults and the elderly for prophylactic treatment of angina pectoris.

4.2 Posology and method of administration

Adults:
One tablet, once daily given in the morning. The dose may be increased to two tablets, the whole dose to be given together (dose range up to 120 mg).
For NITRAX 60 mg only, the dose can be titrated to minimise the possibility of headache by initiating treatment with half a tablet (30 mg) for the first two to four days.
The tablets should not be chewed or crushed and should be swallowed with half a glass of fluid.
Children:
The safety and efficacy of NITRAX prolonged release tablets has not been established.
Elderly:
No need for routine dosage adjustment in the elderly has been found, but special care may be needed in those with increased susceptibility to hypotension or marked hepatic or renal insufficiency.
The lowest effective dose should be used.
Attenuation of effect (tolerance) has occurred in some patients being treated with prolonged release preparations. In such patients intermittent therapy may be more appropriate (see Section 4.4).
Therapy should not be discontinued suddenly. Both dosage and frequency should be tapered gradually (see Section 4.4).
The core of the tablet is insoluble in the digestive juices but disintegrates into small particles when all the active substance has been released. Very occasionally the matrix may pass through the gastrointestinal tract without disintegrating and be found inside the stool, but all active substance has been released.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hypertrophic obstructive cardiomyopathy, constrictive pericarditis, cardiac tamponade, aortic/mitral valve stenosis, severe anaemia, closed-angle glaucoma, conditions associated with raised intracerebral pressure e.g. following head trauma, cerebral haemorrhage. Acute myocardial infarction with low filling pressures, acute circulatory failure (shock, vascular collapse) or very low blood pressure.
Phosphodiesterase type-5 inhibitors e.g. sildenafil, tadalafil and vardenafil have been shown to potentiate the hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contra-indicated (see section 4.5). NITRAX should not be given to patients with a known sensitivity to nitrates.
Concomitant use with the soluble guanylate cyclase stimulator, riociguat, can cause hypotension and is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

NITRAX prolonged release tablets are not indicated for relief of acute anginal attacks. In the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets should be used.
NITRAX should be used with caution in patients who have a recent history of myocardial infarction, or who are suffering from hypothyroidism, hypothermia, malnutrition and severe liver or renal disease.
The lowest effective dose should be used.
Attenuation of effect (tolerance) has occurred in some patients being treated with prolonged release preparations. In such patients intermittent therapy may be more appropriate (see Section 4.2).
Therapy should not be discontinued suddenly. Both dosage and frequency should be tapered gradually (see Section 4.2).
Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina.
Severe postural hypotension with light-headedness and dizziness is frequently observed after the concomitant consumption of alcohol.
NITRAX tablets contain lactose and sucrose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effect of NITRAX may be potentiated by the concomitant administration of drugs with hypotensive effects e.g. beta-blockers, diuretics, ACE-inhibitors, calcium channel blockers, vasodilators, alprostadil, aldesleukin, angiotensin II receptor antagonists and/or alcohol.
The hypotensive effects of nitrates are potentiated by concurrent administration of phosphodiesterase type-5 inhibitors e.g. sildenafil (see section 4.3).
Concomitant use with the soluble guanylate cyclase stimulator, riociguat, can cause hypotension and is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

No data have been reported which would indicate the possibility of adverse effects resulting from the use of isosorbide mononitrate in pregnancy. Safety in pregnancy, however, has not been established. It is not known whether nitrates are excreted in human milk and therefore caution should be exercised when administered to nursing women.
Isosorbide mononitrate should only be used in pregnancy and during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the possible hazards.

4.7 Effects on ability to drive and use machines

The patient should be warned not to drive or operate machinery if hypotension, blurred vision or dizziness occurs.

4.8 Undesirable effects

Throbbing headache may occur when treatment is initiated, but usually disappears after 1-2 weeks of treatment. Hypotension, including postural hypotension, with symptoms such as dizziness, nausea and fatigue has occasionally been reported. Infrequently, flushing and allergic reactions (including rashes) can occur. These symptoms generally disappear during long-term treatment.
Tachycardia and paroxysmal bradycardia have been reported.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Symptoms: Nausea, vomiting, restlessness, warm flushed skin, blurred vision, headache, fainting, tachycardia, hypotension and palpitations. A rise in intracranial pressure with confusion and neurological deficits can sometimes occur.

Management: Consider oral activated charcoal if ingestion of a potentially toxic amount has occurred within 1 hour. Observe for at least 12 hours after the overdose. Monitor blood pressure and pulse. Correct hypotension by raising the foot of the bed and/or by expanding the intravascular volume. Other measures as indicated by the patient's clinical condition. If severe hypotension persists despite the above measures consider use of inotropes such as dopamine or dobutamine.

5. Pharmacological properties
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Organic nitrates. ATC code: C01DA14
Organic nitrates (including GTN, ISDN, and ISMN) are potent relaxers of smooth muscle. They have a powerful effect on vascular smooth muscle with less effect on bronchiolar, gastrointestinal, ureteral and uterine smooth muscle. Low concentrations dilate both arteries and veins.
Venous dilatation pools blood in the periphery leading to a decrease in venous return, central blood volume, and ventricular filling volumes and pressures. Cardiac output may remain unchanged or it may decline as a result of the decrease in venous return. Arterial blood pressure usually declines secondary to a decrease in cardiac output or arteriolar vasodilatation, or both. A modest reflex increase in heart rate results from the decrease in arterial blood pressure. Nitrates can dilate epicardial coronary arteries including atherosclerotic stenoses.
The cellular mechanism of nitrate-induced smooth muscle relaxation has become apparent in recent years. Nitrates enter the smooth muscle cell and are cleaved to inorganic nitrate and eventually to nitric oxide. This cleavage requires the presence of sulphydryl groups, which apparently come from the amino acid cysteine. Nitric oxide undergoes further reduction to nitrosothiol by further interaction with sulphydryl groups. Nitrosothiol activates guanylate cyclase in the vascular smooth muscle cells, thereby generating cyclic guanosine monophosphate (cGMP). It is this latter compound, cGMP, that produces smooth muscle relaxation by accelerating the release of calcium from these cells.

5.2 Pharmacokinetic properties

Absorption:
Isosorbide-5-mononitrate is readily absorbed from the gastro-intestinal tract.
Distribution:
Following oral administration of conventional tablets, peak plasma levels are reached in about 1 hour. Unlike isosorbide dinitrate, ISMN does not undergo first-pass hepatic metabolism and bioavailability is 100%. ISMN has a volume of distribution of about 40 litres and is not significantly protein bound.
Elimination:
ISMN is metabolised to inactive metabolites including isosorbide and isosorbide glucuronide. The pharmacokinetics are unaffected by the presence of heart failure, renal or hepatic insufficiency. Only 20% of ISMN is excreted unchanged in the urine. An elimination half life of about 4-5 hours has been reported.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars
6.1 List of excipients

- Lactose monohydrate
- Sucrose
- Ethylcellulose
- Talc
- Gelatin

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep NITRAX tablets at 25 ° C in the original package, out of the reach of children!

There are no special storage requirements.

6.5 Nature and contents of container

Box of 30 prolonged release tablets of 40 mg isosorbide 5-mononitrate in blister pack (3 blisters x 10 tablets).

Box of 30 prolonged release tablets of 60 mg isosorbide 5-mononitrate in blister pack (3 blisters x 10 tablets).

6.6 Special precautions for disposal and other handling

The treatment with unused medicines and waste materials derived from these medicines is carried out in accordance with the regulations for the handling and disposal of pharmaceutical waste.

7. Marketing authorisation holder

ZADA Pharmaceuticals Ltd.
Donji Bistarac without number
75 300 Lukavac
Bosnia and Herzegovina

8. Marketing authorisation number(s)

Nitrax, 30x40 mg, prolonged release tablets: 04-07.3-1-1816/14
Nitrax, 30x60 mg, prolonged release tablets: 04-07.3-1-1817/14

9. Date of first authorisation/renewal of the authorisation

Nitrax, 30x40 mg, prolonged release tablets: 30.05.2018.
Nitrax, 30x60 mg, prolonged release tablets: 30.05.2018.

10. Date of revision of the text

07.2017.