

COMPOSITION

Esmo[®] LA Capsule: Each long-acting (LA) capsule contains Isosorbide Mononitrate sustained release pellets equivalent to 50 mg Isosorbide Mononitrate BP.

PHARMACOLOGY

While the precise mechanism of action remains unclear, it is probably due to nitric oxide (NO) release which activates guanylate cyclase and increases the synthesis of cyclic GMP. It is possible that NO combines with sulphhydryl groups in the endothelium and produces S-nitrosothiols that stimulate guanylate cyclase production. This is enhanced by N-acetylcysteine which provides a source of sulphhydryl groups. How cyclic GMP produces vascular relaxation is not exactly known. ISMN is released from the pellets contained in this product capsules independently from factors such as pH variability, peristaltic activity or presence of food. Moreover, no differences in pharmacokinetics were also found between healthy volunteers and patients. The relative bioavailability of this product amounts to 80 - 90% when compared to an immediate release preparation. The unique pharmaceutical system of this product accounts for a pharmacokinetic profile that differs essentially from those obtained with other sustained release preparations as demonstrated in a study comparing the pharmacokinetics of this product with sustained-release tablets containing 40 mg or 60 mg ISMN, respectively. While therapeutically effective ISMN plasma concentrations (> 100ng/ml) were achieved with this product within 15-20 minutes after administration, this level was reached with the other ISMN sustained release formulations with a marked delay. The rapid initial rise of plasma concentrations shortly after administration of this product was further confirmed by studies comparing the initial pharmacokinetics and pharmacodynamics after the administration of either a 20 mg immediate release tablet of ISMN or of this product. It was shown that the plasma level profile obtained directly after intake of sustained-release capsules of this product and immediate-release 20 mg tablets, respectively, is comparable. Thus, the onset of anti-ischemic protection can be expected as fast as after taking a 20 mg immediate-release tablet. These findings alone suggest that the onset of action is expected to be earlier than that observed with other ISMN sustained-release formulations.

INDICATIONS

1. Long-term treatment of blood-flow disorders of the coronary vessels (coronary heart disease)
2. Long-term treatment and prophylaxis of angina pectoris (chest pain due to coronary blood-flow disorders of the coronary vessels).
3. Treatment of severe myocardial insufficiency (chronic heart failure) in combination with cardiac glycosides, diuretics, ACE inhibitors, arterial vasodilators.

DOSAGE & ADMINISTRATION

1 capsule once daily.

CONTRAINDICATIONS & PRECAUTIONS

The capsules should not be used in cases of acute myocardial infarction with low filling pressure, acute circulatory failure, shock, vascular collapse, or very low blood pressure.

This product should not be given to patients with a known sensitivity to nitrates, marked anaemia, head trauma, cerebral haemorrhage, severe hypotension or hypovolaemia.

Sildenafil has been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitrates or nitric oxide donors is therefore contraindicated.

SIDE EFFECTS

A headache may occur at the start of treatment, but this usually disappears after a few days. Symptoms of circulatory collapse may arise after the first dose in patients with labile circulation. Symptoms of postural hypotension and syncope may result in some patients. Infrequently (<1% of patients) cases of nausea, vomiting, flushing and allergic rashes can occur.

OVERDOSE

Symptoms and signs: Headache, hypotension, nausea, vomiting, sweating, tachycardia, vertigo and syncope. Methaemoglobinaemia (cyanosis, hypoxaemia, restlessness, respiratory depression, convulsions, cardiac arrhythmias, circulatory failure, raised intracranial pressure) occurs rarely.

Treatment: Symptomatic and supportive measures maintaining airway, breathing and circulation. If ingestion within last 1 hour, administration of activated charcoal. Gastric lavage may also be useful if ingestion within last 1 hour.

DRUG INTERACTIONS

Concurrent intake of drugs with blood pressure lowering properties e.g. beta-blockers, calcium antagonists, vasodilators etc. and/or alcohol may potentiate the hypotensive effect of the capsules. Symptoms of circulatory collapse can arise in patients already taking ACE inhibitors. The hypotensive effect of nitrates is potentiated by concurrent administration of sildenafil. This might also occur with neuroleptics and tricyclic antidepressants.

USE IN PREGNANCY AND LACTATION

There is inadequate evidence of safety of the drug in human pregnancy but nitrates have been used widely in the treatment of angina for many years without apparent ill consequence; animal studies having shown no hazard. Nevertheless it is not advisable to use this drug during pregnancy and lactation.

PEDIATRIC USE

The safety and efficacy of these capsules has yet to be established in children.

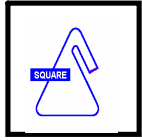
STORAGE CONDITION

Store in a cool and dry place. Protect from light and moisture.

HOW SUPPLIED

Esmo[®] LA Capsule: Each box contains 3x10 long-acting (LA) capsules in blister pack.

® Registered Trade Mark



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PHARMACEUTICALS LTD.
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