

Esmo[®]

Isosorbide Mononitrate
Antianginal

COMPOSITION

Esmo[®] tablet: Each tablet contains Isosorbide Mononitrate BP 20 mg.

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.

It is presumed that at lower doses it also produces dilation of the venous capacitance bed, conducting arteries and coronary collaterals and at higher doses dilates arterioles.

The oral absorption of **Esmo[®]** is rapid (peak concentration occurring by 30 min) and complete. The bioavailability approaches 100%. The volume of distribution at steady state is 48 L. The alpha phase half life is 8.6 min and the beta phase half life is 4.2 hours and is not dose-dependent. The rate of absorption is slowed by food but overall bioavailability is unchanged. It is quite possible that enterohepatic recirculation occurs. Kinetics are not significantly influenced by advancing age, hepatic or renal disease.

Unlike ISDN, ISMN (**Esmo[®]**) is not subject to first pass metabolism in the liver. The volume of distribution is approximately 0.6/kg, and less than 4% is bound to plasma proteins. It is cleared from the serum by denitration to isosorbide (primarily in the liver); glucuronidation to the mononitrate glucuronide; denitration/hydration to sorbitol. None of these metabolites is vasoactive. Less than 1% of administered isosorbide mononitrate is eliminated unchanged in the urine. The overall elimination half-life of ISMN is about 5 hours. The rate of clearance of ISMN is the same in healthy young adults; in patients with various degrees of renal, hepatic, or cardiac dysfunctions and in the elderly.

INDICATIONS

1. *Prophylaxis of angina*

Esmo[®] is an effective prophylactic drug for the relief of exercise-induced angina. The effects become apparent within 1/2 hour oral administration of the drug and last for several hours. However, when given in high doses, tolerance develops rapidly. Although slow release formulations are marketed, controversy surrounds their clinical efficacy, as tolerance may develop within 24 hours of the first dose and the drug may lose effect even at 4 hours during long-term therapy. At present, therapy with a 20 mg dose twice a day at 7 or 8 a.m. and at noon or 2 p.m. is recommended as this regimen does not produce tolerance. However, the patient remains unprotected for several hours due to prolonged nitrate-free intervals.

2. *Congestive heart failure*

Esmo[®], by reducing venous return, lowers elevated end diastolic pressures in the right and left ventricle and improves myocardial function. Cardiac output may either not change or increase, depending upon changes in the afterload. Oral doses of 20-50 mg three or four times daily have been shown to be effective. However, experience with this drug is limited at the present time.

DOSAGE AND ADMINISTRATION

The recommended regimen of **Esmo**[®] tablet is 20 mg (1 tablet) twice daily to be taken orally with an interval of 7 hours. This can be accomplished by taking the first dose on awakening in the morning and the second dose 7 hours later. This dosing regimen provides a daily nitrate-free interval thus avoids development of tolerance or rebound nocturnal angina.

CONTRAINDICATIONS AND PRECAUTION

a. *Absolute*: Obstructive hypertrophic cardiomyopathy, low cardiac output secondary to hypovolaemia, inferior myocardial infarction with right ventricle involvement, raised intracranial pressure, cardiac tamponade.

b. *Relative*: Arterial hypoxaemia and cor pulmonale, Mitral valve prolapse, Glaucoma.

SIDE EFFECT

ISMN is virtually free of toxicological effects unrelated to its action on the cardiovascular system. There are no reports of teratogenic, carcinogenic or mutagenic effects. Symptomatic adverse effects include nausea, vomiting, urinary and faecal incontinence and abdominal pain are uncommon.

CNS: Headache to which tolerance often develops is common; apprehension, restlessness and weakness, vertigo and dizziness are less common. Tachycardia, palpitations and orthostatic hypotension are common symptoms.

DRUG INTERACTION

Orthostatic hypotension may occur with the combined use of calcium channel blockers, antihypertensive agents, phenothiazines and tricyclic antidepressants. Use of alcohol with ISMN may produce severe hypotension and collapse.

USE IN PREGNANCY AND LACTATION

Safety for use during pregnancy has not been established. Use only when clearly needed and when the potential benefits outweigh the unknown potential hazards to the fetus. Safety for use in the nursing mother has not been established. Safety and efficacy for use in infants has not been established.

OVERDOSE

Overdose symptoms include hypotension, tachycardia, warm, flushed skin, headache, palpitations, syncope and increased intracranial pressure with confusion and neurological deficits.

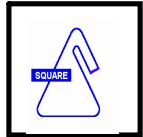
Treatment: Induce emesis or perform gastric lavage followed by charcoal administration. Hypotension is managed by elevating the legs and administration of

intravenous fluids. If necessary a α -adrenergic agonist e.g. methoxamine or phenylephrine may be used. Adrenaline and related β -adrenergic agonists should be avoided.

HOW SUPPLIED

Esmo[®] tablet: Box containing 10x10 tablets in blister pack.

® Registered Trade Mark



**SQUARE
PHARMACEUTICALS LTD.
BANGLADESH**