Effox 20 mg, tablets
Effox 40 mg, tablets
Effox, 25 mg, prolonged release capsules
Effox, 50 mg, prolonged release capsules

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

Each 20 mg tablet contains 20 mg isosorbide mononitrate.

Each 40 mg tablet contains 40 mg isosorbide mononitrate.

Prolonged release capsules

Each 25 mg, prolonged release capsule contains 25 mg isosorbide mononitrate.

Each 50 mg, prolonged release capsule contains 50 mg isosorbide mononitrate.

Excipients

Tablets

lactose monohydrate, microcrystalline cellulose, potato starch, talc, colloidal anhydrous silica, aluminium stearate

Prolonged release capsules

sugar spheres (corn starch and sucrose), lactose monohydrate, poly(O-ethyl) cellulose, talc, hydroxypropylcellulose, polyethylene glycol 20 000. The capsule cap and the capsule body contain: gelatin, titanium dioxide (E 171), iron oxide red (E 172), iron oxide black (E 172)

CLINICAL INFORMATION

Indications

Tablets and prolonged release capsules

For the treatment of:

- Long-term treatment of coronary artery disease.
- Long-term treatment and prevention of angina pectoris (including post myocardial infarction)
- Long-term treatment of chronic congestive heart failure in combination with cardiac glycosides, diuretics, ACE- inhibitors or arterial vasodilators
- Pulmonary hypertension.

Dosage and Administration

All dosage forms should be swallowed whole with water.

The lowest effective dose should be used.

Route of Administration

For oral use

Adults

Tablets 20 mg and 40 mg:

One tablet to be taken at regular time intervals (to allow a nitrate low period) two or three times a day.

For patients not already receiving prophylactic nitrate therapy it is recommended that the initial dose be one tablet of isosorbide mononitrate twice a day.

The dosage may be increased up to 120 mg per day.

Prolonged release capsules 25 mg and 50 mg:

One capsule to be taken in the morning.

For patients with higher nitrate requirements the dose may be increased to two capsules taken simultaneously.

Children

There are no relevant data available.

Elderly

No dose adjustment is required in elderly patients.

Renal and Hepatic impairment

Effox should be used with caution in patients with severely impaired renal or hepatic function.

Contraindications

Effox is contraindicated in:

- Known hypersensitivity to the active substance, to any of the excipients, or to other nitrates or nitrites
- Acute myocardial infarction with low filling pressure
- Low cardiac filling pressures,
- Aortic/mitral valve stenosis
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Constrictive pericarditis
- Cardiac tamponade
- Acute circulatory failure (shock, vascular collapse)
- Very low blood pressure
- Diseases associated with a raised intra-cranial pressure e.g. following a head trauma and including cerebral haemorrhage
- Marked anaemia
- Closed angle glaucoma
- Hypovolaemia
- During nitrate therapy, phosphodiesterase inhibitors (e.g. sildenafil) must not be used, *(see section Interactions)*.

Warnings and Precautions

Effox 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.

Symptoms of circulatory collapse may arise after first dose, particularly in patients with labile circulation.

This product may give rise to postural hypotension and syncope in some patients. Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol.

Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina, (*see section Adverse Reactions)*.

In the event of an acute angina attack, a sublingual treatment such as a GTN spray or tablet should be used instead of isosorbide mononitrate.

If isosorbide mononitrate is not taken as indicated *(see section Dosage and Administration)* tolerance to the medication could develop. The lowest effective dose should be used.

Treatment with isosorbide mononitrate, as with any other nitrate, should not be stopped suddenly. Both the dosage and frequency should be tapered gradually *(see section Dosage and Administration)*

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Due to the presence of sucrose (prolonged release capsules 25 mg, 50 mg), patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Interactions

Phosphodiesterase inhibitors

Phosphodiesterase inhibitors potentiate the anti-hypertensive effect of nitrates and other nitric oxide (NO) donors that can lead to severe refractory hypotension. Therefore the administration of sildenafil, tadalafil or vardenafil is contraindicated during treatment with isosorbide mononitrate, *see section Contraindications*. The patient must be informed of this potential life-threatening interaction.

If phosphodiesterase inhibitors have been administered, the use of isosorbide mononitrate is contraindicated within 24 hours of taking phosphodiesterase inhibitors.

Blood pressure lowering drugs

Concurrent administration of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel blockers, vasodilators, alprostadil, aldesleukin, angiotensin II receptor antagonists etc and/or alcohol may potentiate the hypotensive effect of isosorbide mononitrate. This may also occur with neuroleptics and tricyclic antidepressants.

Dihydroergotamine

Reports suggest that concomitant administration of isosorbide mononitrate may increase the blood level of dihydroergotamine and its hypertensive effect.

Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

Use of isosorbide mononitrate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation

There are no available data on the excretion of isosorbide mononitrate or its metabolites in human breast milk. Therefore, during lactation, isosorbide mononitrate should be used with special caution.

Ability to perform tasks that require judgement, motor or cognitive skills

Dizziness, tiredness or blurred vision might occur at the start of treatment. The patient should therefore be advised that if affected, they should not drive or operate machinery. This effect may be increased by alcohol.

Adverse Reactions

Clinical Trial Data

Not relevant for this product.

Post Marketing Data

Adverse reactions are ranked under headings of frequency using the following convention:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1000 to <1/100

Rare ≥1/10000 to <1/1000

Very rare <1/10000

Not known (cannot be estimated from the available data).

Nervous system disorders

Very common: headache (the incidence of headache diminishes gradually with time and continued use)

Common: light headedness in upright position, dizziness, drowsiness

Cardiac disorders

Common: reflex tachycardia,

Uncommon: severe hypotension may lead to exacerbation of angina pectoris symptoms, *see section Warnings and Precautions*

Not known: paroxysmal bradycardia

Vascular disorders

Common: hypotension on standing

Uncommon: flush, collapse (sometimes accompanied by bradyarrhythmia and syncope)

Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness, pallor and excessive perspiration

Gastrointestinal disorders

Uncommon: nausea, vomiting

Very rare: heartburn

Skin and subcutaneous tissue disorders

Uncommon: allergic skin reactions (e.g. rash)

Not known: exfoliative dermatitis

General disorders and administration site conditions

Common: feeling of weakness

Overdosage

Symptoms and signs

Headache, hypotension, nausea, vomiting, sweating, tachycardia, vertigo, restlessness, warm flushed skin, blurred vision and syncope. A rise in intracranial pressure with confusion and neurological deficits can sometimes occur. Methaemoglobinaemia (cyanosis, hypoxaemia, restlessness, respiratory depression, convulsions, cardiac arrhythmias, circulatory failure, raised intracranial pressure) occurs rarely.

Treatment

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.

If methaemoglobinaemia (symptoms or > 30% methaemoglobin), IV administration of methylene blue 1-2 mg/kg body weight. If therapy fails with second dose after 1 hour or contraindicated, consider red blood cell concentrates or exchange transfusion. In case of cerebral convulsions, diazepam or clonazepam IV, or if therapy fails, phenobarbital, phenytoin or propofol anaesthesia.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group

vasodilatators used in cardiac diseases

Mechanism of Action

Like all organic nitrates, isosorbide mononitrate acts as a donor of nitric oxide (NO). NO causes a relaxation of vascular smooth muscle via the stimulation of guanylyl cyclase and the subsequent increase of intracellular cyclic guanosine monophosphate (cGMP) concentration. A cGMP-dependent protein kinase is thus stimulated, with resultant alteration of the phosphorylation of various proteins in the smooth muscle cell. This eventually leads to the dephosphorylation of the light chain of myosin and the lowering of smooth muscle tone.

Pharmacodynamic effects

Isosorbide mononitrate causes a relaxation of vascular smooth muscle thereby inducing a vasodilatation.

Both, peripheral arteries and veins are relaxed by isosorbide mononitrate. The latter effect promotes venous pooling of blood and decreases venous return to the heart, thereby reducing ventricular end-diastolic pressure and volume (preload).

The action on arterial, and at higher dosages arteriolar vessels, reduces the systemic vascular resistance (afterload). This in turn reduces the cardiac work.

The effects on both preload and afterload lead subsequently to a reduced oxygen consumption of the heart.

Furthermore, isosorbide mononitrate causes redistribution of blood flow to the subendocardial regions of the heart when the coronary circulation is partially occluded by arteriosclerotic lesions. This latter effect is likely to be due to a selective dilation of large coronary vessels. Nitrate induced dilation of collateral arteries can improve the perfusion of poststenotic myocardium. Nitrates also dilate eccentric stenoses as they can counteract possible constricting factors acting on the residual arch of compliant smooth muscle at the site of the coronary narrowing. Furthermore, coronary spasms can be relaxed by nitrates.

Nitrates were shown to improve resting and exercise hemodynamics in patients suffering from congestive heart failure. In this beneficial effect several mechanisms including an improvement of valvular regurgitation (due to the lessening of ventricular dilatation) and the reduction of myocardial oxygen demand are involved.

By decreasing the oxygen demand and increasing the oxygen supply, the area of myocardial damage is reduced. Therefore, isosorbide mononitrate may be useful in selected patients who have had a myocardial infarction. Effects on other organ systems include a relaxation of the bronchial muscle, the muscles of the gastrointestinal, the biliary and the urinary tract. Relaxation of the uterine smooth muscles is reported as well.

Pharmacokinetics

Absorption

Isosorbide mononitrate is rapidly and completely absorbed after oral administration. After intake of isosorbide mononitrate 20mg or 40mg the bioavailability is 90–100%. The bioavailability of the slow release preparations is 80–90% compared to an immediate release tablet. Food does not significantly affect absorption.

Distribution

The apparent volume of distribution is about 50:1, implying that isosorbide mononitrate is distributed mainly in total body water.

Cmax for tablets 20 mg or 40 mg is seen about one hour after administration.

Prolonged release capsules 25 mg, 50 mg contain pellets formulated to release 30 % of the dose immediately, whilst 70 % of the dose is released slowly.

Metabolism

Isosorbide mononitrate is extensively metabolised to NO and isosorbide; while the first is the active agent, the latter is inactive.

Elimination

Elimination half-life was determined to be between 4 and 5 h.

Special patient populations

Other patient characteristics

Evidence was provided that the plasma profiles in healthy volunteers and patients suffering from chronic stable angina are similar.

Isosorbide mononitrate is dialysable.

Incompatibilities

There are no relevant data available.

Packaging:

Effox 20mg tablet: Cartoon Box of 2 strips each of 10 tablets

Effox 40 mg tablet: Cartoon Box of 2 strips each of 10 tablets

Effox 25 mg caps: Cartoon Box of 1,2,3 strips each of 10 capsules

Effox 50 mg caps: Cartoon Box of 2 strips each of 10 capsules

Patient instruction:

Keep out of reach of children

Store at temperature not exceeding 30^{o}C

GlaxoSmithKline

MINAPHARM