SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isosorbide Mononitrate 40 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40 mg of isosorbide mononitrate.

Excipient(s) with known effect: Each 40 mg tablet contains 160 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Isosorbide mononitrate tablets 40 mg are indicated for use in the treatment and prophylaxis of angina pectoris and as adjunctive therapy in congestive heart failure which does not respond adequately to cardiac glycosides and/or diuretics.

4.2. Posology and method of administration

For oral administration.

Adults
The recommended dosage is from 20 to 120 mg isosorbide mononitrate daily in divided doses. The majority of patients will require a dosage in the range of 40 to 60 mg daily in divided doses. The tablets should be taken with fluid and swallowed whole without chewing.

The lowest effective dose should be used.

For patients who have not previously received prophylatic nitrate therapy an initial dosage of 10 mg isosorbide mononitrate (1 tablet) daily for 2 days followed by a dosage of 20 mg (1 tablet morning and evening) for a further 3 days is recommended. Subsequently the daily dosage may be increased to the normal prophylatic level. Patients already accustomed to chronic nitrate therapy normally may be transferred directly to a therapeutic dose.

For those previously treated with isosorbide dinitrate in conventional form the dosage of isosorbide mononitrate should be the same initially. Isosorbide mononitrate is effectively twice as potent as sustained release forms of isosorbide dinitrate and patients transferred from such treatment should receive isosorbide mononitrate at half the previous dosage.

Therapy should not be discontinued suddenly. Both dosage and frequency should be tapered gradually (see section 4.4)

Children
The safety and efficacy of isosorbide mononitrate has not been established in children.

The elderly
There is no evidence to suggest that an adjustment of the dosage is necessary. However, caution may be required in elderly patients who are known to be susceptible to the effects of hypotensive medication.

Renal and hepatic impairment
No dosage reduction is necessary.

4.3. Contraindications

Isosorbide mononitrate tablets are contra-indicated in patients with a known hypersensitivity to isosorbide mononitrate other nitrates or to any of the excipients or other nitrates., in cases of marked low blood pressure (BP ≤ 90mm Hg systolic), acute circulatory failure (shock), circulatory collapse, cardiogenic shock and acute myocardial infarction with low left ventricular filling pressure, hypertrophic obstructive cardiomyopathy, constrictive pericarditis, cardiac tamponade, low cardiac filling pressures, aortic/mitral valve stenosis, and conditions associated with raised intracranial pressure e.g. following head trauma and cerebral haemorrhage.

Isosorbide mononitrate should not be used in patients with marked anaemia, severe hypotension, closed angle glaucoma or hypovolaemia.

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 contraindicated (see section 4.5).

4.4. Special warnings and precautions for use

Caution should be exercised in patients suffering from hypothyroidism, malnutrition, severe renal or hepatic impairment, hypothermia and recent history of myocardial infarction.

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 alcholol.

Hypotension induced by nitrates may be accompanied by paradoxical bradycardia and increased angina.

Isosorbide mononitrate is not indicated for relief of an acute angina attack; in the event of an acute angina attack, sublingual or buccal glyceryl trinitrate tablets or spray should be used.

If the tablets are not taken as indicated (see section 4.2.) tolerance to the medication could develop. The lowest effective dose should be used (see section 4.2).

Since a rebound phenomenon cannot be excluded, 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 4.2)

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5. Interactions with other medicinal products and other forms of interaction

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.

In particular, the hypotensive effects of nitrates are potentiated by the concurrent administration of phosphodiesterase type-5 inhibitors (e.g. sildenafil) which are used for erectile dysfunction (see section 4.4 and 4.3). This might lead to life threatening cardiovascular complications. Patients who are on isosorbide mononitrate therapy therefore must not use phosphodiesterase type-5 inhibitors

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

4.6. Fertility, pregnancy and lactation

Pregnancy
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.

Breastfeeding
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 hazards.

4.7. Effects on ability to drive and use machines

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.

4.8. Undesirable effects

Nervous system disorders:
A very common (>10% of patients) adverse reaction to isosorbide mononitrate is throbbing headache. The incidence of headache diminishes gradually with time and continued use.
Occasionally, particularly when first used, slight states of dizziness or feeling of weakness may occur, which normally improve during treatment.

Cardiac disorders:
At the beginning of treatment or when the dose is increased, hypotension and / or light headedness in the upright position are commonly observed (i.e in 1 – 10% of patients). (including postural hypotension). These symptoms may be associated with dizziness, drowsiness, reflex tachychardia and a feeling of weakness.

Tachycardia and paroxysmal bradycardia have been reported.

Infrequently (i.e. in less than 1% of patients) flushing may occur.

Severe hypotensive responses have been reported for organic nitrates and include nausea, vomiting, restlessness pallor and excessive perspiration. Uncommonly, collapse may occur (sometimes accompanied by bradyarrhythmias and syncope).

Vascular disorders
Uncommonly severe hypotension may lead to enhanced angina symptoms.

Administration of isosorbide mononitrate may produce transient hypoxaemia as a result of redistribution of blood flow with a relative increase in perfusion of poorly ventilated areas of the lung. This may cause ischaemia in patients with coronary heart disease.

Formation of methaemoglobin might occur, in particular in susceptible patients such as those with methaemoglobin reductase deficiency.

Gastrointestinal disorders:
Infrequently (i.e. in less than 1% of patients), especially when first used, gastro-intestinal symptoms, nausea, vomiting may occur.

A few reports of heartburn most likely due to a nitrate induced sphincter relaxation have been recorded.

Skin and subcutaneous tissue disorders:
Infrequently (i.e. in less than 1% of patients) allergic skin reaction (e.g. rash) may occur sometimes severely. In single cases exfoliative dermatitis may occur.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

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.

Management: Consider oral activated charcoal if ingestion of a potentially toxic amounts 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 patients's clinical condition. If severe hypotension persists despite the above measures consider use of inotropes such as dopamine or dobutamine.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: CO1D A14 Vasodilators used in cardiac diseases (organic nitrates)

Isosorbide mononitrate is an organic nitrate which, in common with other cardioactive nitrates, is a vasodilator. It produces decreased left and right ventricular end-diastolic pressures to a greater extent than the decrease in systemic arterial pressure, thereby reducing afterload and especially the preload of the heart. Isosorbide mononitrate provides long term nitrate treatment of angina pectoris and heart failure in a form with complete biological availability due to lack of any significant hepatic first-pass metabolism. This provides consistently uniform blood levels of drug substance and a predictable clinical response. The onset of activity occurs within 20 minutes, and depending on dosage, is maintained for up to 10 hours.

Isosorbide mononitrate influences the oxygen supply to ischaemic myocardium by causing the redistribution of blood flow along collateral channels and from epicardial to endocardial regions by selective dilation of large epicardial vessels.

Beta-blocking drugs have a different pharmacological action in angina and may have a complementary effect when co-administered with isosorbide mononitrate.

It reduces the requirement of the myocardium for oxygen by increasing venous capacitance, causing a pooling of blood in peripheral veins, thereby reducing ventricular volume and heart wall distension and arises the antianginal effect. The main effect of isosorbide mononitrate is to produce a marked venous vasodilation without a significant effect on the systemic arteries. The venous dilation leads to an accumulation of blood in the capacitance vessels resulting in a reduction of venous return to the heart. This results in a reduction of the ventricular diastolic volume, which produces a reduction in intramural tension (afterload) as well as reductions of filling pressures and pulmonary capillary pressure (preload).

5.2. Pharmacokinetic properties

Isosorbide mononitrate displays 100% bioavailability on oral administration. Consequently, serum levels are predictable.

Isosorbide-5-mononitrate is rapidly absorbed and peak plasma levels occur approx. 1 hour following oral dosing.

Isosorbide-5-mononitrate is completely bioavailable after oral doses and is not subject to pre-systemic elimination processes.

Isosorbide-5-mononitrate is eliminated from the plasma with a half-life of about 5.1 hours. It is metabolised to Isosorbide-5-MN- 2-glucoronide, which has a half-life of approximately 2.5 hours. As well as being excreted unchanged in the urine.

After multiple oral dosing plasma concentrations are similar to those that can be predicted from single dose kinetic parameters.

The drug is eliminated solely by the liver and therefore can be used in renal insufficiency.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, oncogenicity and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablets contain:
Microcrystalline cellulose (E460)
Povidone K29-32 (E1201)
Sodium starch glycolate
Magnesium stearate (E572)
Lactose

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 25°C. Store in the original blister package.

6.5. Nature and contents of container

Blister strips (in multiples of 10, 14 or 20 tablets) in packs of 10, 14, 28, 30, 50, 56, 60 or 100 tablets.

HDPE or polypropylene containers with caps or child resistant closures in packs of 28, 30, 50, 56, 60, 100, 250, 500 or 1000 tablets.

Not all pack sizes may be marketed.

6.6 Instruction for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0288

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 November 1994.

10. DATE OF REVISION OF THE TEXT

07/11/2022

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