

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ISOSORBIDE DINITRATE TABLETS BP 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg Isosorbide Dinitrate PhEur.

Excipient with known effect:

Each tablet contains 152.4mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white uncoated tablets.

White to off-white, circular, flat bevelled-edge uncoated tablets impressed “C” on one face and the identifying code “IT” and “10” on either side of a central division line on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- 1) Prophylaxis and treatment of angina pectoris.
- 2) As an adjunctive treatment in the management of severe acute or chronic congestive cardiac failure.

4.2. Posology and method of administration

Posology

Adults

- *Angina:* 30-120mg daily in divided doses according to individual requirements. Dosage should be gradually increased to minimise the possibility of nitrate headache and/or tolerance.
- *Congestive cardiac failure:* In severe congestive cardiac failure doses of 40-160mg, daily in divided doses may be employed depending on individual requirements. The optimum dosage is best determined by continuous haemodynamic monitoring. The use of isosorbide dinitrate tablets in severe congestive cardiac failure should be regarded as an adjunctive therapy to more conventional treatment (*e.g.* cardiac glycosides, diuretics).

The maximum daily dose should not exceed 240mg in divided doses.

Elderly

- Dosage may be reduced in the elderly especially where there is impairment of renal or hepatic function.

Paediatric population

- The safety and efficacy of isosorbide dinitrate has yet to be established in children.

Method of Administration

For oral administration

4.3. Contraindications

Hypersensitivity to the active substance, other nitrates or to any of the excipients listed in section 6.1.

This product should not be given to patients with a known sensitivity to nitrates, very low blood pressure, acute myocardial infarction with low filling pressure, marked anaemia, head trauma, cerebral haemorrhage, acute circulatory failure, severe hypotension or hypovolaemia.

Phosphodiesterase inhibitors (e.g. sildenafil) have been shown to potentiate the hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contraindicated.

During nitrate therapy, the soluble guanylate cyclase stimulator riociguat must not be used (see section 4.5).

4.4. Special warnings and precautions for use

Use with caution in patients with closed-angle glaucoma (increased intra-ocular pressure).

These tablets should be used with caution in patients who are suffering from hypothyroidism, hypothermia, malnutrition, severe liver disease or renal disease.

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

This product may give rise to symptoms of postural hypotension and syncope in some patients.

These tablets should be used with particular caution and under medical supervision in the following:

- Low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure).
- Reducing systolic blood-pressure below 90 mmHg must be avoided patients with aortic/mitral valve stenosis.

Hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, cardiac tamponade, low cardiac filling pressures, aortic/mitral valve stenosis, and diseases associated with raised intracranial pressure.

Treatment with these tablets must not be interrupted or stopped to take phosphodiesterase inhibitor products due to the increased risk of inducing an attack of angina pectoris.

If these tablets are not taken as indicated, tolerance to the medication could develop.

Hypoxaemia

Caution should be exercised in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure. As a potent vasodilator, ISDN could result in

increased perfusion of poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

During treatment with ISDN alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of ISDN (see section 4.5).

Excipients

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

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

Concurrent intake of drugs with blood pressure lowering properties e.g. beta-blockers, calcium antagonists, vasodilators, ACE-inhibitors, monoamine oxidase inhibitors etc. and/or alcohol may potentiate the hypotensive effect of the tablets. Symptoms of circulatory collapse can arise in patients already taking ACE inhibitors.

The concurrent intake of ISDN with ACE-inhibitors or arterial vasodilators could be a desirable interaction unless the antihypertensive effects are excessive in which case consider reducing the dose of one or both drugs.

The hypotensive effect of nitrates is potentiated by concurrent administration of phosphodiesterase inhibitors (e.g. sildenafil). This might also occur with neuroleptics and tricyclic antidepressants.

Reports suggest that when administered concomitantly, nitrates may increase the blood level of dihydroergotamine and its hypertensive effect.

Saproterin (Tetrahydrobiopterine, BH₄) is a cofactor for nitric oxide synthetase. Caution is recommended during concomitant use of saproterin-containing medicine with all agents that cause vasodilation by affecting nitric oxide (NO) metabolism or action, including classical NO donors (e.g. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN), isosorbide mononitrate (ISMN) and others).

The use of isosorbide dinitrate with riociguat, a soluble guanylate cyclase stimulator, is contraindicated (see section 4.3) since concomitant use can cause hypotension.

4.6. Fertility, pregnancy and lactation

Pregnancy and breast-feeding

This product should not be used during pregnancy or lactation unless considered essential by the physician.

Fertility

There is no data available on the effect of ISDN on fertility in humans.

4.7. Effects on ability to drive and use machines

Headaches, tiredness and dizziness may occur. These may affect the ability to drive and operate machinery. Patients should not drive or operate machinery if their ability is impaired.

4.8. Undesirable effects

Undesirable effects frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

System organ class	Frequency	Adverse reaction
Endocrine disorders	Very rare	pituitary apoplexy in patients with undiagnosed pituitary tumours
Nervous system disorders	Very common	headache
	Common	dizziness, somnolence
Eye disorders	Very rare	angle closure glaucoma
Cardiac disorders	Common	tachycardia
	Uncommon	angina pectoris aggravated
Vascular disorders	Common	orthostatic hypotension, symptoms/signs of cerebral ischaemia, peripheral oedema
	Uncommon	circulatory collapse (sometimes accompanied by bradyarrhythmia and syncope)
	Not known	hypotension
Gastrointestinal disorders	Uncommon	nausea, vomiting
	Very rare	heartburn
Skin and subcutaneous tissue disorders	Uncommon	allergic skin reaction (e.g. rash), flushing
	Very rare	angioedema, Stevens-Johnson Syndrome
	Not known	exfoliative dermatitis
General disorders and administration site conditions	Common	asthenia

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

During treatment with these tablets, a temporary hypoxaemia may occur due to a relative redistribution of the blood flow in hypoventilated alveolar areas. Particularly in patients with coronary artery disease this may lead to a myocardial hypoxia.

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

- Fall of blood pressure ≤ 90 mm Hg, paleness, sweating, weak pulse, tachycardia, light-headedness on standing, headache, weakness, dizziness, nausea and vomiting.

- During isosorbide mononitrate biotransformation nitrite ions are released, which may include methaemoglobinaemia and cyanosis with subsequent tachypnoea, anxiety, loss of consciousness and cardiac arrest. It cannot be excluded that an overdose of isosorbide dinitrate may cause this adverse reaction.
- In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

Management

- Stop intake of the drug.
- General procedures in the event of nitrate-related hypotension:
 - Patient should be kept horizontal with the head lowered and legs raised
 - Supply oxygen
 - Expand plasma volume
 - For specific shock treatment admit patient to intensive care unit.
- Specific Procedures:
 - Raising the blood pressure if the blood pressure is very low
 - Treatment of methaemoglobinaemia (reduction therapy of choice with vitamin C, methylene-blue, or toluidine-blue; administer oxygen (if necessary); initiate artificial ventilation; haemodialysis (if necessary)).
- Resuscitation measures:
 - In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiac diseases. organic nitrates, ATC code: C01D A08

Pharmacodynamics

Isosorbide dinitrate causes a relaxation of vascular smooth muscle thereby inducing a vasodilation.

Both peripheral arteries and veins are relaxed by isosorbide dinitrate. 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, reduce the systemic vascular resistance (afterload). This in turn reduces the cardiac work.

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

Furthermore, isosorbide dinitrate causes redistribution of blood flow to the subendocardial regions of the heart when the coronary circulation is partially occluded by arteriosclerotic lesions. This last 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 haemodynamics 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 dilation) 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 dinitrate may be useful in selected patients who suffered 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.

Mechanism of action

Like all organic nitrates, isosorbide dinitrate 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 contractility.

5.2. Pharmacokinetic properties

After administration of one tablet of ISDN 20mg at least two peak concentrations of ISDN occurred in the plasma. The initial peak (mean 1.9 ng/ml, range 1.0 to 3.4 ng/ml) occurred during 0.5 to 2 hours and then the mean plasma concentrations declined to 1.3 ng/ml at 3 hours. The concentration then increased again to reach a major peak level (mean 6.2 ng/ml range 1.6 to 12.3 ng/ml) during 4 to 6 hours after dosing. Plasma concentrations of ISDN have been measured after administration of increasing doses in the range 20 to 100 mg as ISDN 20mg tablets. Means of peak concentrations of 4.2 ng/ml, 13.1 ng/ml, 20.7 ng/ml, 36.8 ng/ml and 34.9 ng/ml were measured after doses of 20mg, 40mg, 60mg, 80mg and 100mg respectively.

Gastrointestinal absorption is slower than absorption through the oral mucosa. The first pass effect is higher when given orally.

Isosorbide dinitrate is metabolised to isosorbide 2-mononitrate with a half-life of 2.01 h (± 0.4 h) to 2.5 h and isosorbide 5-mononitrate with a half-life of 4.6 h (± 0.8 h). Both metabolites are pharmacologically active.

The relative bioavailability of ISDN in comparison to the non-sustained-release tablet amounts to more than 80% after oral use.

5.3. Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Also contains: magnesium stearate, maize starch, lactose, polyvidone.

6.2. Incompatibilities

None known.

6.3. Shelf life

Shelf-life

Three years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4. Special precautions for storage

Store below 25°C in a dry place.

6.5. Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil.

Pack sizes: 28s, 56s, 60s, 84s, 90s, 100s, 112s, 1000s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6. Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8. MARKETING AUTHORISATION NUMBER

PL 0142/0321

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

April 1993

10 DATE OF REVISION OF THE TEXT

29/09/2023