

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Isosorbide Dinitrate Injection Concentrate 1mg/ml, 10ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide Dinitrate 10mg in 10ml.

3. PHARMACEUTICAL FORM

Clear, colourless, sterile aqueous solution intended for parenteral administration to human beings.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Isosorbide dinitrate is indicated in the treatment of unresponsive left ventricular failure of various aetiology, including left ventricular failure secondary to acute myocardial infarction. It is also indicated in the management of severe or unstable angina pectoris.

4.2. Posology and Method of Administration

Recommended Route : Intravenously, after dilution.

Adults, including the elderly: The dose must be adjusted according to the patients response. A dose of between 2 and 12mg per hour is generally suitable, although doses as high as 20mg per hour may be necessary.

Children: The safety and efficacy of isosorbide dinitrate injection has not been established in children.

Administration: This is a concentrated solution and should never be administered in bolus form. It should be administered only as an admixture, intravenously, with a suitable vehicle such as Sodium Chloride Injection B.P. or Dextrose Injection B.P. Admixtures are prepared by exchanging the required volume of Isosorbide Dinitrate Injection Concentrate with an equal

volume of the infusion vehicle. For example, if the dose requirement is 6mg per hour, 50ml of Isosorbide Dinitrate Injection Concentrate should be added to 450ml of the infusion vehicle. The admixture now contains 1mg in 10ml and the required dosage can be achieved by administering 60ml per hour (equivalent to 20 standard drops or 60 paediatric microdrops per minute).

If further reduction in fluid intake is required, 100ml of Isosorbide Dinitrate Injection Concentrate made up to 500ml with a suitable infusion vehicle produces an admixture containing 2mg in 10ml which may be infused at a drip rate of 30ml per hour for a required dosage of 6mg per hour.

Where fluid intake is strictly limited, a dilution of 50% is advocated to produce a solution containing 0.5mg in 1ml.

Admixtures should be made up under aseptic conditions. Loss of potency will occur on contact with PVC and the use of PVC infusion bags or administration sets should, therefore, be avoided.

4.3 Contraindications

These are common to all nitrates: hypersensitivity to isosorbide dinitrate, other nitrates or any of the excipients, marked anaemia, cerebral haemorrhage, head trauma, diseases associated with an increased intracranial pressure, hypovolaemia, severe hypotension (systolic blood pressure less than 90mmHg), aortic and/or mitral valve stenosis, closed angle glaucoma.

Use in circulatory collapse or low filling pressure is also contraindicated.

Isosorbide Dinitrate Injection Concentrate 1mg/ml should not be used in the treatment of cardiogenic shock (unless some means of maintaining an adequate diastolic pressure are undertaken), hypertrophic obstructive cardiomyopathy, cardiac tamponade, or constrictive pericarditis.

Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) have been shown to potentiate the hypotensive effects of nitrates. Therefore, Isosorbide Dinitrate Injection Concentrate 1mg/ml must not be given to patients receiving phosphodiesterase-5 inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Isosorbide dinitrate should be used with caution and under medical supervision in patients who are suffering from:

- hypothyroidism,
- hypothermia,
- malnutrition,
- severe hepatic or renal disease
- orthostatic syndrome

The development of tolerance (decrease in efficacy) as well as cross tolerance towards other nitrate-type drugs (decrease in effect incase of a prior therapy with another nitrate drug) has been described. For a decrease in, or loss of, effect to be prevented, continuously high dosages must be avoided.

Blood pressure and pulse rate should always be monitored and the dose adjusted according to the patient's response.

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 etc. and /or alcohol may potentiate the hypotensive effect of Isosorbide Dinitrate Injection Concentrate 1mg/ml. This might also occur with neuroleptics and tricyclic antidepressants.

Also phosphodiesterase-5 inhibitors e.g. sildenafil, potentiate the hypotensive effect of Isosorbide Dinitrate Injection Concentrate 1mg/ml. This might lead to life-threatening cardiovascular complications, see section 4.3.

Reports suggest that, when administered concomitantly, Isosorbide Dinitrate Injection Concentrate 1mg/ml may increase the blood level of dihydroergotamine and its hypertensive effect.

4.6. Pregnancy and Lactation

Although there are no reported data to indicate the possibility of adverse effects resulting from administration of isosorbide dinitrate in pregnancy, safety in pregnancy has not been established. Isosorbide dinitrate should only be used in pregnancy or lactation if, in the opinion of the physician, the possible benefits outweigh the possible risks.

4.7 Effects on ability to drive and use machines

As for other drugs which produce changes in blood pressure, patients taking Isosorbide Dinitrate Injection Concentrate 1mg/ml should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

4.8. Undesirable Effects

As with all nitrates, the vasodilatory effects may cause a fall in systemic arterial pressure which could give rise to symptoms of cerebral flow insufficiency or decreased coronary perfusion. In common with other nitrates, headache, severe hypotension, nausea and retching, excessive sweating, apprehension, restlessness, muscle twitching, retrosternal discomfort,

palpitations, abdominal pain, syncope and bradycardia may occur during therapy with isosorbide dinitrate (particularly if infused too rapidly). Methaemoglobinaemia has been known to occur, rarely. If methaemoglobinaemia is diagnosed, treatment with methylene blue at a dose of 1 to 2 mg/kg intravenously may be administered, depending on the degree and rapidity of methaemoglobin formation.

4.9. Overdose

Toxic effects of overdose include: vomiting, restlessness, cyanosis, hypertension, tachycardia and syncope.

Overdosage or too rapid infusion, especially in heart failure will result in excessively reduced filling pressures, hypotension, decreased ventricular performance and decreased perfusion of tissues. If the arterial systolic blood pressure drops below 90mm Hg and if the heart rate increases above 10% of its initial value, the infusion should be discontinued. Where necessary, hypotension may be treated by keeping the patient recumbent in a shock position and/or use hypertensive agents such as methoxamine or phenylephrine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Isosorbide dinitrate is a member of the organic nitrate group of vasodilators. It decreases both preload and afterload as a result of respective dilatation of venous capacitance and arteriolar resistance vessels. In left ventricular failure, isosorbide dinitrate produces a significant increase in the ejection fraction, stroke volume, cardiac output and tissue perfusion.

Isosorbide dinitrate decreases myocardial oxygen demand by increasing the venous capacitance and thereby reducing ventricular end-diastolic pressure and volume. It also influences oxygen supply, by improving the distribution of the myocardial blood flow to the subendocardial regions.

5.2. Pharmacokinetic Properties

The biotransformation of organic nitrates is the result of reductive hydrolysis catalysed by the hepatic enzyme glucathione-organic nitrate reductase. The major route of metabolism of isosorbide dinitrate in man is by enzymatic denitration followed by formation of glucuronides. The primary initial metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, have

longer half lives (2 - 5 hours) and are presumed to be responsible, at least in part, for the therapeutic efficacy of isosorbide dinitrate.

Denitration markedly reduces its activity. Hepatic denitration is also influenced by hepatic disease and blood flow. The terminal elimination half life is 54.7 minutes following intravenous injection. The total plasma clearance is 136 litres per hour.

5.3. Pre-clinical Safety Data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium Chloride B.P.
Sodium Hydroxide B.P.
Water for Injections B.P.

6.2. Incompatibilities

Isosorbide dinitrate is incompatible with infusion bags and giving sets made from PVC - loss of potency will occur on contact with PVC.

6.3. Shelf-Life

3 years (36 months).

6.4. Special Precautions for Storage

Protect from light.
Store below 30°C.

6.5. Nature and Contents of Container

10ml, clear glass ampoules, glass type 1 Ph.Eur., packed in cardboard cartons to contain 10 x 10ml ampoules.

6.6. Instructions for Use/Handling

Solutions containing visible solid particles should not be used.
Dilute before use with a suitable vehicle such as Sodium Chloride Intravenous Infusion.
Not for direct injection.
For administration by I.V. Infusion only.
Use by slow infusion only, with haemodynamic monitoring of the patient.
Use as directed by the physician.
Keep out of reach of children.
If only part used, discard the remaining solution.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER

PL 2848/0160.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

25/10/1991.

10. DATE OF REVISION OF THE TEXT

27/07/2010