Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isosorbide Dinitrate Injection Concentrate 10 mg in 10 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml of the concentrate solution contains 10 mg of Isosorbide Dinitrate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
Clear, colourless, sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The indications for Isosorbide Dinitrate Injection Concentrate are:

1. Treatment of unresponsive left ventricular failure secondary to acute myocardial infarction.
2. Unresponsive left ventricular failure of various aetiology.
3. 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 patient's 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 Concentrate have 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 BP or Dextrose Injection BP. 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 a maximum reduction in fluid intake is required, a dilution of 50% is advocated to produce a solution containing 0.5mg in 1ml (5mg in 10ml). This may be administered by slow intravenous infusion using a syringe pump. A desired dose of 6mg per hour would require an infusion rate of 12ml per hour.

Isosorbide Dinitrate Injection Concentrate is compatible with glass or polyethylene delivery systems.

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

Patients with a known hypersensitivity to nitrates.
Patients with marked anaemia, head trauma, cerebral haemorrhage, severe hypotension or hypovolaemia.
Cardiogenic shock, unless some means of maintaining an adequate diastolic pressure is undertaken, for example by concurrent administration of an inotrope. Use in circulatory collapse or in low filling pressure. The hypotensive effects of nitrates are potentiated by sildenafil, and their co-administration is contra-indicated.

4.4 Special warnings and precautions for use

Close monitoring of the pulse and blood pressure is essential during infusion of isosorbide dinitrate and the dose should be adjusted according to the patient's response.
Isosorbide dinitrate should be used with caution in patients who are predisposed to closed angle glaucoma or to patients with hypothyroidism, hypothermia, malnutrition, severe hepatic or renal disease.
Isosorbide dinitrate should be administered by means of a micro-drip set, infusion pump or similar device, which permits maintenance of constant infusion rate.

4.5 Interaction with other medicinal products and other forms of interaction

Isosorbide dinitrate may potentiate the effects of antihypertensive drugs.

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

Not relevant, as patients would be too ill to engage in these activities.

4.8 Undesirable effects

In common with other nitrates, headache and nausea, syncope and bradycardia may occur during therapy with isosorbide dinitrate.
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 decrease coronary perfusion.
Methaemaglobinaemia has been known to occur, rarely. If methaemaglobinaemia 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 methaemaglobin formation.

4.9 Overdose

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 of hypertensive agents.

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

Isosorbide dinitrate is subject to a large first-pass effect by the liver, where it is enzymatically metabolised to the active intermediates isosorbide-2-mononitrate and isosorbide-5-mononitrate, the latter being the major metabolite with a reported terminal elimination half life of 54.7 minutes following intravenous injection.

5.3 Preclinical 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
Sodium Hydroxide
Water for injections

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^{o}C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

7 MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd.
Roscrea
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 73/123/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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June 2002