SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Isosorbide Dinitrate 0.1% w/v Concentrate for Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 1mg of isosorbide dinitrate (0.1%w/v).
Each 10ml ampoule contains 10mg of isosorbide dinitrate and 36mg of sodium.
Each 50ml vial contains 50mg of isosorbide dinitrate and 180mg of sodium.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of unresponsive left ventricular failure, secondary to acute myocardial infarction.

- Unresponsive left ventricular failure of various aetiologies.

- Severe or unstable angina pectoris.

- To facilitate or prolong balloon inflation and to prevent or relieve coronary spasm during
  percutaneous transluminal coronary angioplasty.

4.2 Posology and method of administration

Dosage: Adults, including the elderly.

Isosorbide Dinitrate is a concentrated solution. It should never be injected directly and must be diluted.

Avoid administration through PVC or PU tubing and giving sets, because of adsorption of ISDN onto plastic.

Intravenous administration: Dosage should be adjusted according to patient response. Typically, a dose of between 2mg and 12mg per hour is suitable, although doses of up to 20mg per hour may be necessary.

Prepared admixtures are always given by intravenous infusion or using a syringe pump incorporating a glass or rigid plastic syringe (see section 6.6). The patient's blood pressure and pulse should be monitored closely during administration.

Intracoronary administration: A dilution of 50% is recommended. The usual dose is 1mg given as a bolus injection prior to balloon inflation. Additional doses may be given, not exceeding 5mg over 30 minutes.

The safety and efficacy of Isosorbide Dinitrate has not been established in children.

Isosorbide Dinitrate is presented in 10mL ampoules and 50mL vials intended for single use only.

4.3 Contraindications

Use of Isosorbide Dinitrate is contraindicated in patients with known hypersensitivity to nitrates, marked anaemia, cerebral haemorrhage, head trauma, diseases associated with an increased intracranial pressure, hypovolaemia, severe hypotension (systolic

blood pressure less than 90mm Hg), aortic and/or mitral valve stenosis, closed angle glaucoma.

Isosorbide Dinitrate must not be used in cases of circulatory collapse or low filling pressure.
Treatment of cardiogenic shock with Isosorbide Dinitrate should only be undertaken if means of maintaining an adequate diastolic pressure is available.
Isosorbide Dinitrate should not be used in the treatment of hypertrophic obstructive cardiomyopathy, constrictive pericarditis or cardiac tamponade. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) have been shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitrates or nitric oxide donors is therefore contraindicated (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
- malnutrition
- severe liver or renal disease
- hypothermia
- orthostatic syndrome

The development of tolerance (decrease in efficacy) as well as cross tolerance towards other nitrate-type drugs (decrease in effect in case 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.
Isosorbide Dinitrate contains 0.15mmol (3.6mg) of sodium per mL and should be taken into consideration by patients on a controlled sodium diet.

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. This might also occur with neuroleptics and tricyclic antidepressants.

Also phosphodiesterase-5 inhibitors e.g. sildenafil, potentiate the hypotensive effects of isosorbide dinitrate. This might lead to life-threatening cardiovascular complications, see section 4.3.

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

4.6 Fertility, Pregnancy and lactation

The safety of this medicinal product for human use in pregnancy has not been established. However, no data have been reported that suggest adverse effects occur as a result of using isosorbide dinitrate during pregnancy. Isosorbide dinitrate should only be used during pregnancy and lactation if the benefits of treatment outweigh the possible hazards.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

During administration of Isosorbide Dinitrate the following undesirable effects may be observed:
Nervous system disorders: headache, dizziness, somnolence.
Cardiac disorders: tachycardia, angina pectoris aggravated.
Vascular disorders: orthostatic hypotension, collapse (sometimes accompanied by bradyarrhythmia and syncope).
Gastrointestinal disorders: nausea, vomiting, heartburn.

Skin and subcutaneous tissue disorders: allergic skin reactions (e.g. rash), flush, angioedema, Stevens-Johnson-Syndrome, in single cases: exfoliative dermatitis.
General disorders and administration site conditions: asthenia
Severe hypotensive responses have been reported for organic nitrates including nausea, vomiting, restlessness, pallor, and excessive perspiration. During treatment with Isosorbide Dinitrate a temporary hypoxemia 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 at: 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 mmHg
- Pallor
- Sweating
- Weak pulse
- Tachycardia
- Postural dizziness
- Headache
- Asthenia
- Dizziness
- Nausea
- Vomiting
- Diarrhoea
- Methaemoglobinaemia has been reported in patients receiving other organic nitrates. During isosorbide dinitrate biotransformation nitrite ions are released, which may induce 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.

General procedure:

- Stop delivery of the drug
- General procedures in the event of nitrate-related hypotension:
  - The patient must be laid down with lowered head and raised legs
  - Supply oxygen
  - Expand plasma volume (i.v. fluids)
  - Specific shock treatment (admit patient to intensive care unit)

Special procedure:
- Raise the blood pressure if the blood pressure is very low.
- Additional administration of noradrenaline or other vasoconstrictors.
- Treatment of methaemoglobinaemia
  - Reduction therapy of choice with vitamin C, methylene-blue, or toluidine-blue
  - Administer oxygen (if necessary)
  - Initiate artificial ventilation
- Resuscitation measures

In case of signs of respiratory and circulatory arrest, initiate resuscitation measures immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code : C01D A08 Vasodilators used in cardiac diseases – organic nitrates

Isosorbide dinitrate 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 dinitrate 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 dilatation of large epicardial vessels.

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.

5.2 Pharmacokinetic properties

Isosorbide dinitrate (ISDN) is eliminated from plasma with a short half-life (about 0.7 h). The metabolic degradation of ISDN occurs via denitration and glucuronidation, like all organic nitrates. The rates of formation of the metabolites has been calculated for isosorbide-5- mononitrate (IS-5-MN) with 0.57 h^{-1} followed by isosorbide-2-mononitrate (IS-2-MN) with 0.27 h^{-1}, and isosorbide (IS) with 0.16 h^{-1}. IS-5-MN and IS-2-MN are the primary metabolites which are also pharmacologically active. IS-5-MN is metabolised to isosorbide 5-mononitrate-2-glucuronide (IS-5-MN-2-GLU). The half-life of this metabolite (about 2.5 h) is shorter than that of IS-5-MN (about 5.1 h). The half-life of ISDN is the shortest of all and that of IS-2-MN (about 3.2 h) lies in between.

5.3 Preclinical safety data

Acute toxicity:

Acute toxicity of isosorbide dinitrate was related to an exaggerated

pharmacodynamic effect. Animal studies showed good local tolerability of the undiluted isosorbide dinitrate solution.

Chronic toxicity:

In chronic oral toxicity studies in rats and dogs, toxic effects including CNS symptoms and an increase in liver weight, were observed at exposures considered sufficiently in excess of the maximum human exposure levels indicating little relevance to clinical use.

Reproduction studies:

There is no evidence from animal studies suggesting a teratogenic effect of isosorbide dinitrate. At high maternally toxic oral doses, isosorbide dinitrate was associated with increased post-implantation loss and reduced survival of offspring.

Mutagenicity and carcinogenicity:

No evidence for mutagenic effect was found in both in vitro and in vivo tests. A long-term study in rats did not provide any evidence for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

The use of polyvinyl chloride (PVC) or polyurethane (PU) giving sets and containers should be avoided as significant losses of the active ingredient by adsorption can occur.
Materials made of polyethylene (PE), Polypropylene (PP) or polytetrafluroethylene (PTFE) have been proven to be suitable for infusing this medicine.
This medicinal product must not be mixed with other medicinal product except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 24 months.
After first opening: once opened, the product should be used immediately and any unused drug discarded.
Isosorbide dinitrate solutions diluted with sodium chloride or glucose have been shown to be chemically and physically stable for 72 hours at 25°C, when stored in polypropylene or glass containers, protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep container (ampoules or vials) in the outer carton to protect from light.

6.5 Nature and contents of container

Isosorbide Dinitrate 0.1% w/v Concentrate for Solution for Injection or Infusion is presented in 10mL clear Type I glass ampoules and in 50mL vials made from clear Type II glass, sealed with a bromobutyl rubber stopper and an aluminium tamper proof flip-top cap. The product is packed into cartons containing 10 ampoules, 1 vial or 10 vials. Both pack sizes of vials may not be available at the same time.

6.6 Special precautions for disposal

The injection is for single dose use only.

The injection should not be used if particles are present.

Isosorbide Dinitrate is a concentrate. Once opened, the product should be used immediately and any unused drug discarded.

Isosorbide Dinitrate is compatible with commonly employed infusion fluids. It is compatible with glass infusion bottles and infusion packs made from polyethylene (PE), Polypropylene (PP) or polytetrafluroethylene (PTFE). A syringe pump with a glass or plastic syringe may also be used for infusion.

Example of admixture preparation

To obtain a dose of 6 mg per hour, add 50 mL of Isosorbide Dinitrate to 450 mL of a suitable vehicle, under aseptic conditions. The resultant admixture (500 mL) contains 100 μg/mL (1mg/10mL) isosorbide dinitrate. An infusion rate of 60mL per hour (equivalent to 60 paediatric microdrops per minute or 20 standard drops per minute) will deliver the required dose of 6mg per hour.

Should it be necessary to reduce fluid intake, 100mL of Isosorbide Dinitrate may be diluted to 500mL using a suitable vehicle. The resultant solution now contains 200 μg/mL (2mg/10mL) isosorbide dinitrate. An infusion rate of 30mL per hour (equivalent to 30 paediatric microdrops per minute or 10 standard drops per minute), will deliver the required dose of 6 mg per hour.

A dilution of 50% is advocated to produce a solution containing 0.5 mg/mL where fluid intake is strictly limited.

7 MARKETING AUTHORISATION HOLDER

Torbay Pharmaceuticals Limited,
Wilkins Drive,
Paignton,
Devon, TQ4 7FG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 56021/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/06/2010

10 DATE OF REVISION OF THE TEXT

24/12/2025