

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Monocord 20, 40
Monocord 50 SR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Monocord 20: Each tablet contains 20 mg of isosorbide mononitrate.

Excipients with known effect:

Each tablet contains 114.6 mg lactose monohydrate.

Each tablet contains approximately 59 mg sucrose.

Monocord 40: Each tablet contains 40 mg of isosorbide mononitrate.

Excipients with known effect:

Each tablet contains 229.2 mg lactose monohydrate.

Each tablet contains approximately 117 mg sucrose.

Monocord 50 SR: Each slow release tablet contains 50 mg isosorbide mononitrate.

Excipients with known effect:

Each tablet contains 86.5 mg lactose monohydrate.

Each tablet contains approximately 86 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Monocord 20, 40: Tablets.

Monocord 20: Purple, film coated, biconvex tablets, scored on one side.

Monocord 40: White, round, film coated tablets, scored on one side.

The tablets can be divided into equal halves.

Monocord 50 SR: slow release tablets.

Monocord 50 SR: Red, round, film coated tablets, without a score.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

For the treatment of angina pectoris and prevention of angina attacks.

Monocord 20, 40 are also indicated for the treatment of congestive heart failure.

4.2 Posology and method of administration

Posology

Monocord 20, 40:

Adults

One tablet to be taken asymmetrically (to allow a nitrate low period) two times a day. The dosage may be increased up to 120 mg per day. Dosage regime should be designed according to the clinical response of the patient.

Tablets should be taken with water on an empty stomach about an hour before or two hours after a meal.

The lowest effective dose should be used.

In patients taking Monocord twice daily, the second dose should be taken 8 hours after the 1st dosage.

Elderly

There is no evidence to suggest that an adjustment of the dosage is necessary in elderly.

Paediatric population

The safety and efficacy of Monocord has yet to be established in children.

Treatment with Monocord, as with any other nitrate, should not be stopped suddenly.

Both the dosage and frequency should be tapered gradually (see section 4.4).

Monocord 50 SR:

Adults

One tablet to be taken in the morning. The dose may be increased up to two tablets per day, to be taken together in the morning, for patients with higher nitrate requirements. Dosage regime should be designed according to the clinical response of the patient.

Tablets must be swallowed whole with water, on an empty stomach about an hour before or two hours after a meal. The tablets must not be divided, chewed or crushed.

The lowest effective dose should be used.

Elderly

There is no evidence to suggest that an adjustment of the dosage is necessary in elderly.

Paediatric population

The safety and efficacy of Monocord 50 SR has yet to be established in children.

Attenuation of effect has occurred in some patients being treated with slow release preparations. In such patients intermittent therapy may be more appropriate (see section 4.4).

Treatment with Monocord 50 SR, as with any other nitrate, should not be stopped suddenly.

Both the dosage and frequency should be tapered gradually (see section 4.4).

Method of administration

For oral administration.

4.3 Contraindications

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

Monocord should not be used in cases of acute myocardial infarction with low filling pressure, acute circulatory failure (shock, vascular collapse), or very low blood pressure (systolic blood pressure below 90 mmHg), hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, cardiac tamponade, low cardiac filling pressures, aortic/mitral valve stenosis and diseases associated with a raised intra-cranial pressure e.g. following a head trauma and including cerebral haemorrhage.

Monocord should not be used in patients with severe anaemia, severe hypotension, closed angle glaucoma or severe 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 4.4 and 4.5).

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

This product may give rise to symptoms of postural hypotension and syncope in some patients. Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol.

Monocord should be used with caution in patients who have a recent history of myocardial infarction low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure), or orthostatic dysfunction.

Reducing systolic blood-pressure below 90 mmHg must be avoided.

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

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

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

Monocord tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Monocord tablets also contain sucrose and therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

In the event of an acute angina attack, a sublingual treatment such as a GTN spray or tablet should be used instead of Monocord tablets. The onset of action of Monocord is not sufficiently rapid to be useful to treat an acute anginal attack.

If the tablets are not taken as indicated (see section 4.2) tolerance to the medication could develop. In some patients being treated with slow release preparations, attenuation of effect is observed. In such patients, intermittent therapy may be more appropriate. The lowest effective dose should be used.

Treatment with Monocord, as with any other nitrate, should not be stopped suddenly.

Both the dosage and frequency should be tapered gradually (see section 4.2).

In patients with decreased gastrointestinal transit time, a decrease in release of the active ingredient may occur.

Patients who undergo a maintenance treatment with Monocord should be informed that they must not use phosphodiesterase inhibitor-containing products (e.g. sildenafil, tadalafil, vardenafil).

Monocord therapy should not be interrupted to take phosphodiesterase inhibitor containing products (e.g. sildenafil, tadalafil, vardenafil), because the risk of inducing an attack of angina pectoris could increase by doing so (see section 4.3 and 4.5).

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, isosorbide mononitrate 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 isosorbide mononitrate alcohol should be avoided as it may potentiate the hypotensive effect of isosorbide mononitrate (see section 4.5).

4.5 Interaction 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, ACE-inhibitors, monoamine oxidase inhibitors, angiotensin II receptor antagonists etc. and/or alcohol may potentiate the hypotensive effect of Monocord. This may also occur with neuroleptics and tricyclic antidepressants.

The concurrent intake of isosorbide mononitrate 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.

Any blood pressure lowering effect of Monocord will be increased if used together with phosphodiesterase type-5 inhibitors which are used for erectile dysfunction (see 4.3 and 4.4). This might lead to life threatening cardiovascular complications. Patients who are on Monocord therapy therefore must not use phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil).

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

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

Sapropterine (Tetrahydrobiopterine, BH₄) is a cofactor for nitric oxide synthetase.

Caution is recommended during concomitant use of sapropterine-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 5-mononitrate (5-ISMN) and others).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established for isosorbide mononitrate. There is data that nitrates are excreted in breast milk and may cause methemoglobinemia in infants. Therefore Monocord should only be used in pregnancy and during lactation if, in the opinion of the physician, the possible benefits of treatment outweigh the hazards.

Breast-feeding

The extent of excretion of isosorbide mononitrate in human breast milk has not been determined. Therefore caution should be exercised when administered to nursing women.

Fertility

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

4.7 Effects on ability to drive and use machines

Dizziness, tiredness or blurred vision might occur at the start of treatment. If affected, do not drive or operate machinery. This effect may be increased by alcohol.

4.8 Undesirable effects

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

During administration of Monocord the following undesirable effects may be observed:

Nervous system disorders:

- very common: headache
- common: dizziness (including dizziness postural), somnolence

Cardiac disorders:

- common: tachycardia
- uncommon: angina pectoris aggravated

Vascular disorders:

- common: orthostatic hypotension
- 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 reactions (e.g. rash), flushing
- not known: dermatitis exfoliative

Immune system disorders:

- not known: angioedema

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 Monocord, 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

4.9 Overdose

Animal experience:

In rats and mice, significant lethality at oral doses of 1965 mg/kg and 2581 mg/kg, respectively, was observed.

Human experience:

Symptoms:

- Fall of blood pressure \leq 90 mmHg
- Paleness
- Sweating
- Weak pulse
- Tachycardia
- Light-headedness on standing
- Headache
- Weakness
- Dizziness
- Nausea
- Vomiting
- Diarrhoea

Methaemoglobinaemia has been reported in patients receiving other organic nitrates.

During isosorbide mononitrate 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 mononitrate may cause this adverse reaction.

In very high doses the intracranial pressure may be increased. This might lead to cerebral symptoms.

General procedure:

- Stop intake of the drug
- General procedures in the event of nitrate-related hypotension

- Patients should be kept horizontal with the head lowered and legs raised
- Supply oxygen
- Expand plasma volume (i.v. fluids)
- Specific treatment for shock (admit patient to intensive care unit)

Special procedure:

- 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
 - Hemodialysis (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, ATC Code: C01DA14

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 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.

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.

Mechanism of action

Like all organic nitrates, isosorbide mononitrate 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 smooth muscle tone.

5.2 Pharmacokinetic properties

Immediate release tablets:

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-glucuronide 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.

Slow release formulation:

Isosorbide mononitrate is rapidly absorbed following oral administration. The bioavailability is 80-90% when compared to the immediate release isosorbide mononitrate tablets.

Isosorbide mononitrate is extensively metabolised to nitric oxide (NO – which is the active agent) and isosorbide (inactive). In patients with cirrhotic disease or cardiac failure or renal failure, pharmacokinetic parameters were similar to those obtained in healthy volunteers.

Characteristics in patients:

Evidence was provided that the plasma profiles in healthy volunteers and patients suffering from chronic stable angina are similar.

Isosorbide mononitrate is dialysable.

5.3 Preclinical safety data

Acute toxicity:

Studies on acute toxicity in mice and rats with different routes of administration indicate a low acute toxicity (LD50 oral approximately 2,000 - 2,500 mg/kg b.w.).

Chronic toxicity:

Long term toxicity has been tested in rats for 78 weeks and in dogs for 52 weeks.

First toxic reactions occurred in dosages of 90 mg/kg (dog) and 405 mg/kg (rat), respectively. Thus taking into account the recommended dosage of 20 to 30 mg/d in humans, the therapeutic index can be stated as high.

Reproduction studies:

These studies included a fertility and breeding study over two generations in rats; teratology studies in rats and rabbits; and a rat peri-postnatal study. The dosage levels used were generally high and produced maternal toxic effects at the highest dose. No teratogenic effects of isosorbide mononitrate were observed.

Mutagenicity:

Isosorbide mononitrate was tested in different studies both in vitro and in vivo (Ames test, Human peripheral lymphocytes, Bone marrow of rats and hamsters, V 79 test, SCE test) on possible mutagenic effects. As all tests were negative the mutagenic risk in humans is considered low.

Carcinogenicity:

Neither the long term toxicity studies in rats and dogs nor a special carcinogenicity study, performed in rats over 125 weeks (males) and 138 weeks (females), indicated neoplastic properties of isosorbide mononitrate. Therefore, it can be concluded that the carcinogenic risk in humans is low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monocord 20, 40:

Lactose monohydrate, compressible sugar, sodium starch glycolate, hypromellose, magnesium stearate, titanium dioxide (E171), silica colloidal anhydrous, macrogol 400, carnauba wax.

Monocord 20 also contains: Indigo carmine aluminum lake (E132), erythrosine aluminum lake (E127).

Monocord 40 also contains: Copovidone.

Monocord 50 SR:

Hypromellose, compressible sugar, lactose monohydrate, magnesium stearate, titanium dioxide (E171), silica colloidal anhydrous, erythrosine aluminum lake (E127), quinoline yellow aluminum lake (E104), macrogol 400, indigo carmine aluminum lake (E132), carnauba wax.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister.

Pack sizes:

Monocord 20: 10, 28, 30, 50, 60 tablets.

Monocord 40: 10, 28, 30, 50 tablets.

Monocord 50 SR: 10, 28, 30, 50 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORIZATION NUMBERS

Monocord 20: 052-51-23128-00

Monocord 40: 049-99-26415-00

Monocord 50 SR: 050-88-26416-00

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