

NEW ZEALAND DATA SHEET

CORANGIN® Isosorbide-5-mononitrate

Trade name

CORANGIN® 40 mg and 60 mg slow release divisible tablets

Description and composition

Pharmaceutical forms

Slow-release tablets , divisible (Divitabs®), containing 40 or 60 mg isosorbide-5-mononitrate.

Active substance

Isosorbide-5-mononitrate. One tablet contains 40 mg or 60 mg.

Active moiety

Isosorbide-5-mononitrate.

Excipients

Tablets (40 mg, 60 mg): silicagel, aerosil 200, lactose, magnesium stearate, Methocel K 100 M premium (hydroxypropyl-methylcellulose), polyethylenglycol 4000, polyvinylpyrrolidon K 30.

Indications

Corangin is indicated for:

- Long term treatment of ischemic heart disease,
- Prevention of angina pectoris attacks, and also in cases where symptoms of angina pectoris persist after myocardial infarction. Corangin may be used either as monotherapy or in combination with other antianginal agents (e.g. beta-blockers or calcium antagonists).
- Treatment for chronic heart failure, in combination with digitalis or other positive-inotropic agents and/or diuretics.

Dosage and administration

General rules

Corangin is not intended for the immediate relief of acute attacks of angina pectoris; if they occur, the additional use of rapid-acting nitrate preparations is indicated.

Development of tolerance or attenuation of effect may occur with all long-acting nitrates in individual patients on continuous treatment. This can be reversed with low-nitrate blood levels (as observed with Corangin at the end of the dosing interval).

Angina pectoris

The starting dose should be 1 tablet of Corangin 40 mg once daily and increased as required, either by adding one-half of a 40 mg tablet or changing to the 60 mg tablet. Depending on the time of day at which the angina pectoris attacks occur in the individual patient, the slow-release tablet can be taken either in the morning or in the evening.

If treatment with Corangin in angina pectoris patients is to be discontinued, an abrupt cessation should be avoided: if a change to another product is envisaged, a period of overlapping treatment should be considered.

Chronic heart failure

In chronic heart failure, it is recommended that treatment be started in hospital and the patient's hemodynamic status monitored; treatment should also be continued in hospital until the required maintenance dose has been established. The optimal dose should be determined based on the clinical response and tolerability, with careful monitoring for signs of overdosage such as hypotension and tachycardia.

Dosage and administration in special populations

Pediatrics

No information is available on the use of Corangin in children.

Geriatrics (aged 65 years or above)

In elderly patients, Corangin should be started at a low dose and with caution due to the higher likelihood of orthostatic or postural hypotension.

Renal impairment

No dose adjustment of Corangin is required in patients with renal impairment (see [Clinical pharmacology](#)).

Hepatic impairment

No dose adjustment of Corangin is required in patients with hepatic impairment (see [Clinical pharmacology](#)).

Method of administration

Corangin is taken orally and can be administered with or without food (see [Clinical Pharmacology](#)).

Corangin is presented in the form of Divitabs. These are divisible slow-release tablets, which allow the dosage to be increased or decreased stepwise, so that it can be more closely adapted to individual requirements. Even if the two halves of the tablet are ingested separately, the prolonged duration of action remains unchanged.

Contraindications

- Known hypersensitivity to nitrates.
- Acute circulatory failure associated with marked hypotension (shock, states of collapse).
- Conditions associated with elevated intracranial pressure.
- Myocardial insufficiency due to obstruction (e.g. in the presence of aortic or mitral valve stenosis or of constrictive pericarditis).
- Concomitant use of Corangin and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil is contraindicated, because PDE5 inhibitors may amplify the vasodilatory effects of Corangin resulting in severe hypotension.

Warnings and precautions

Cardiac and vascular disorders

In cases of recent myocardial infarction or acute heart failure, Corangin should only be used cautiously under strict medical surveillance and/or hemodynamic monitoring.

Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, isosorbide-5-mononitrate could reverse this protective vasoconstriction and thus 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.

Treatment discontinuation

When transferring the patient on long-term therapy to another form of medication, Corangin should be gradually withdrawn and overlapping treatment should be started to avoid the risk of angina pectoris.

Driving and using machines

As syncope and dizziness are the known adverse drug reactions associated with the use of Corangin, patients should not drive a vehicle or operate a machine or perform tasks that require alertness if they experience these symptoms.

Adverse drug reactions

Table 7.1 presents adverse drug reactions observed from mixed sources including clinical trials and post-marketing spontaneous reports.

Table 0-1 **Tabulated summary of adverse drug reactions**

Cardiac disorders	
Unknown	Syncope, orthostatic hypotension, tachycardia, dizziness, flushing
Gastrointestinal disorders	
Unknown	Vomiting, nausea
Nervous system disorders	
Unknown	Headache

Like other nitrate preparations, Corangin may frequently give rise to headache, which is due to cerebral vasodilatation and is dose dependent. Headaches, however, usually regress after a few days despite continuation of the therapy. Flushing, syncope, dizziness, and orthostatic hypotension, which may be associated with reflex-induced tachycardia, have rarely been reported.

Interactions

Interactions resulting in a contraindication

Sildenafil

Concomitant use of Corangin and PDE5 inhibitors such as sildenafil is contraindicated; because sildenafil may amplify the vasodilatory effects of Corangin resulting in severe hypotension (see [Contraindications](#)).

Interactions to be considered

Antihypertensive drugs

Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, may potentiate the blood-pressure-lowering effect of Corangin.

CNS depressants

Tricyclic antidepressants, or major tranquilizers, as well as the consumption of alcohol, may potentiate the blood-pressure-lowering effect of Corangin.

Dihydroergotamine

Concurrent administration of Corangin with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitrates and may lead to coronary vasoconstriction.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The possibility that acetylsalicylic acid and NSAIDs might diminish the therapeutic response to Corangin cannot be excluded.

Women of child bearing potential, pregnancy, breast-feeding and fertility

Women of child bearing potential

There is no data supporting any special recommendations in women of child-bearing potential.

Pregnancy

There is a limited amount of data from the use of isosorbide-5-mononitrate in pregnant patients. Limited animal studies do not indicate direct or indirect harmful effects with respect

to reproductive toxicity. Corangin should be given to a pregnant woman only if clearly needed and the benefit outweighs the risk.

Breast-feeding

It is not known whether the active substance passes into the breast milk. The benefits for the mother must be weighed against the risks for the child.

Fertility

There is no data available on the effect of isosorbide-5-mononitrate on fertility in humans.

Overdosage

Signs and symptoms

High doses of isosorbide-5-mononitrate may lead to more pronounced systemic side effects, e.g. to a marked hypotension or to syncope. Excessive dosage of all nitrates may, on rare occasions, provoke methemoglobinemia.

Treatment

Overdosage should be treated symptomatically.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmaco therapeutic group: Vasodilator (ATC code C01DA14)

Mechanism of action

Nitrates are prodrugs that are sources of nitric oxide (NO). NO activates the soluble isoform of guanylyl cyclase, thereby increasing intracellular levels of cyclic guanosine monophosphate (cGMP). In turn, cGMP promotes the dephosphorylation of the myosin light chain and the reduction of cytosolic calcium which leads to the relaxation of smooth muscle cells, ultimately leading to vasodilation .

Pharmacodynamics (PD)

Like other nitrates, isosorbide-5-mononitrate is suitable for the chronic treatment of ischemic heart disease and heart failure. In angina pectoris, its fundamental mechanism of action is primarily based on an increase in venous capacitance (venous pooling) leading to a decreased return of blood to the heart. Owing to this phenomenon, left-ventricular end-diastolic pressure (preload) and hence filling volume diminishes, resulting in a decreased myocardial oxygen requirement at rest and especially during exercise, with an improvement in exercise capacity in patients with angina pectoris. In the coronary arterial circulation, isosorbide-5-mononitrate dilates both extramural conductance and small resistance vessels. The drug appears to cause a redistribution of coronary blood flow to the ischemic subendocardium by selectively dilating large epicardial vessels. It also produces relaxation of vasospasm, whether spontaneous or induced by ergometrine.

In addition, isosorbide-5-mononitrate exerts a dose-dependent dilating effect on the arteriolar vascular bed, as a result of which systemic vascular resistance (afterload) and left-ventricular systolic wall tension decrease, leading to a reduction in myocardial oxygen consumption.

In chronic heart failure the dilating action exerted by isosorbide-5-mononitrate on the veins lowers the elevated left-ventricular filling pressure, while at the same time cardiac output either remains unchanged or increases slightly.

Isosorbide-5-mononitrate proves effective especially in patients with severe heart failure showing prominent signs and symptoms of venous pulmonary congestion due to a pronounced increase in left-ventricular filling pressure. If an increase in cardiac output is desired, combined treatment with an arterial vasodilator is recommended.

The duration of action of isosorbide-5-mononitrate is longer than that of its parent compound. A therapeutic efficacy similar to that of isosorbide dinitrate may be achieved with approximately half the dose.

Pharmacokinetics (PK)

Absorption

Isosorbide-5-mononitrate is rapidly and completely absorbed from the conventional dosage forms. Unlike isosorbide dinitrate, isosorbide-5-mononitrate is free from first-pass metabolism in the liver, and its bioavailability therefore shows lower inter-individual variability. AUC values assessed by reference to the plasma levels increase linearly with the dose.

With Corangin, the peak concentrations attained are approximately 60% lower than after administration of the same dose in conventional dosage forms. Peak concentrations are reached 4-8 hours after ingestion of Corangin and in less than 1 hour after administration of conventional formulations. The amount absorbed from sustained-release formulations such as Corangin is slightly reduced (by 10-20%) in comparison with conventional formulations. No accumulation of isosorbide-5-mononitrate was seen after repeated once-daily administration in normal volunteers or in patients. The results of pharmacokinetic studies suggest that no alterations of the dosage should be necessary in patients with coronary heart disease, renal failure, or hepatic cirrhosis. Ingestion of food has been reported to have only a negligible effect on the absorption of isosorbide-5-mononitrate.

Distribution

The volume of distribution of isosorbide mononitrate is approximately 0.6 L/kg, which is close to the total body water. The plasma protein binding of isosorbide mononitrate is negligible.

Biotransformation/ Metabolism

Isosorbide mononitrate is almost completely metabolized in the liver. The resulting metabolites are inactive.

Elimination

Isosorbide mononitrate is excreted via the kidneys almost exclusively in the form of metabolites. Approximately 2% is excreted via the kidneys in unchanged form. Mean half-lives of isosorbide-5-mononitrate calculated after administration of conventional formulations range between 4.0 and 4.8 hours.

Clinical studies

No recent clinical trials have been conducted with Corangin.

Non- clinical safety data

Several in vitro and in vivo test systems revealed no evidence of mutagenic activity of isosorbide-5-mononitrate. A dietary carcinogenicity study in rats gave no evidence of a carcinogenic potential of isosorbide-5-mononitrate. The effect of Corangin on reproduction and embryonic, fetal and/or postnatal development has been insufficiently investigated in animals.

Pharmaceutical information

Incompatibilities

None known.

Special precautions for storage

Store at below 25°C. Protect from moisture.

Corangin should be kept out of the reach of children.

Instructions for use and handling

PVC/PE/PVDC blisters of 30 tablets

Medicines classification

Prescription Medicine

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