# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

ISOKET RETARD 20 TABLETS

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains isosorbide dinitrate 20 mg in a prolonged release formulation.

Excipients with known effect: 157.95 mg lactose monohydrate

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prolonged release tablets.

White with break score, marked IR 20 on the upper side and with SCHWARZ PHARMA on the reverse side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the prophylaxis and treatment of angina pectoris.

### 4.2 Posology and method of administration

Posology

*Adults:* One tablet to be taken twice daily without chewing and with a sufficient amount of fluid. The second dose should be given 6 to 8 hours after the first dose. For patients with higher nitrate requirements the dose may be increased to one tablet three times daily, but ensuring a 12 hours treatment free interval every 24 hours.

*Elderly population:* Clinical experience has not necessitated alternative advice for use in elderly patients.

*Paediatric population:* The safety and efficacy of Isoket Retard has yet to be established.

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.

This product should not be given to patients with a known sensitivity to nitrates, very low blood pressure, acute myocardial infarction with low filling pressure, marked anaemia, head trauma, cerebral haemorrhage, acute circulatory failure, severe hypotension or hypovolaemia.

Phosphodiesterase inhibitors (e.g. Sildenafil) have been shown to potentiate the hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contraindicated.

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

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

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

This product may give rise to symptoms of postural hypotension and syncope in some patients.

These tablets should be used with particular caution and under medical supervision in the following:

- Low filling pressures e.g. in acute myocardial infarction, impaired left ventricular function (left ventricular failure).
- Reducing systolic blood-pressure below 90 mmHg must be avoided patients with aortic/mitral valve stenosis

Hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, cardiac tamponade, low cardiac filling pressures, aortic/mitral valve stenosis, and diseases associated with raised intracranial pressure.

Treatment with these tablets must not be interrupted or stopped to take phosphodiestearase inhibitor products due to the increased risk of inducing an attack of angina pectoris

If these tablets are not taken as indicated with the appropriate dosing interval (see section 4.2) tolerance to the medication could develop.

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, ISDN 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 ISDN alcohol should be avoided as it may potentiate the hypotensive and vasodilating effect of ISDN (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 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, ACE-inhibitors, monoamine oxidase inhibitors etc. and/or alcohol may potentiate the hypotensive effect of the tablets. Symptoms of circulatory collapse can arise in patients already taking ACE inhibitors.

The concurrent intake of ISDN 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.

The hypotensive effect of nitrates is potentiated by concurrent administration of phosphodiesterase inhibitors (e.g. sildenafil). This might also occur with neuroleptics and tricyclic antidepressants.

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

Saproterin (Tetrahydrobioterine, BH4) is a cofactor for nitric oxide sythetase. Caution is recommended during concomitant use of saproterin-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 mononitrate (ISMN) and others).

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

## 4.6 Fertility, pregnancy and lactation

**Pregnancy and lactation**

This product should not be used during pregnancy or lactation unless considered essential by the physician.

**Fertility**

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

## 4.7 Effects on ability to drive and use machines

Headaches, tiredness, dizziness may occur. These may affect the ability to drive and operate machinery. Patients should not drive or operate machinery if their ability is impaired.

## 4.8 Undesirable effects

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

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

Nervous system disorders:
Very common: headache
Common: dizziness, 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 reaction (e.g. rash), flushing
Very rare: angioedema, Stevens-Johnson- Syndrome
Not known: exfoliative dermatitis

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 these tablets, a temporary hypoxaemia 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, 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 ≤ 90mm Hg, paleness, sweating, weak pulse, tachycardia, light-headedness on standing, headache, weakness, dizziness, nausea and vomiting.
- During isosorbide mononitrate biotransformation nitrite ions are released, which may include methaemoglobinaemia and cyanosis with subsequent tachypnoea, anxiety, loss of consciousness and cardiac arrest. It can not 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.

Supportive measures:

- Stop intake of the drug
- General procedures in the event of nitrate-related hypotension:
  - Patient should be kept horizontal with the head lowered and legs raised
  - Supply oxygen
  - Expand plasma volume
  - For specific shock treatment admit patient to intensive care unit

Specific Procedures:

- Raising the blood pressure if the blood pressure is very low
- Treatment of methaeglobinaemia
  - 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. organic nitrates, ATC code: C01D A08

Pharmacodynamics:

Isosorbide dinitrate causes a relaxation of vascular smooth muscle thereby inducing a vasodilation.

Both peripheral arteries and veins are relaxed by isosorbide dinitrate. The latter effect promotes venous pooling of blood and decreases venous return to the heart, thereby reducing ventricular end-diastolic pressure and volume (preload).

The action on arterial, and at higher dosages arteriolar vessels, reduce the systemic vascular resistance (afterload). This in turn reduces the cardiac work.

The effect on both preload and afterload lead subsequently to a reduced oxygen consumption of the heart.

Furthermore, isosorbide dinitrate causes redistribution of blood flow to the subendocardial regions of the heart when the coronary circulation is partially occluded by arteriosclerotic lesions. This last effect is likely to be due to a selective dilation of large coronary vessels. Nitrate-induced dilation of collateral arteries can improve the perfusion of poststenotic myocardium. Nitrates also dilate eccentric stenoses as they can counteract possible constricting factors acting on the residual arch of compliant smooth muscle at the site of the coronary narrowing. Furthermore, coronary spasms can be relaxed by nitrates.

Nitrates were shown to improve resting and exercise haemodynamics in patients suffering from congestive heart failure. In this beneficial effect several mechanisms including an improvement of valvular regurgitation (due to the lessening of ventricular dilation) and the reduction of myocardial oxygen demand are involved.

By decreasing the oxygen demand and increasing the oxygen supply, the area of myocardial damage is reduced. Therefore, isosorbide dinitrate may be useful in selected patients who suffered a myocardial infarction.

Effects on other organ systems include a relaxation of the bronchial muscle, the muscles of the gastrointestinal, the biliary and the urinary tract. Relaxation of the uterine smooth muscles is reported as well.

Mechanism of action:
Like all organic nitrates, isosorbide dinitrate 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 contractility

## 5.2 Pharmacokinetic properties

After administration of one tablet of Isoket Retard 20 at least two peak concentrations of ISDN occurred in the plasma. The initial peak (mean 1.9 ng/ml, range 1.0 to 3.4 ng/ml) occurred during 0.5 to 2 hours and then the mean plasma concentrations declined to 1.3 ng/ml at 3 hours. The concentration then increased again to reach a major peak level (mean 6.2 ng/ml range 1.6 to 12.3 ng/ml) during 4 to 6 hours after dosing. Plasma concentrations of ISDN have been measured after administration of increasing doses in the range 20 to 100 mg as Isoket Retard 20 tablets. Means of peak concentrations of 4.2 ng/ml, 13.1 ng/ml, 20.7 ng/ml, 36.8 ng/ml and 34.9 ng/ml were measured after doses of 20mg, 40mg, 60mg, 80mg and 100mg respectively.

Gastrointestinal absorption is slower than absorption through the oral mucosa. The first pass effect is higher when given orally. Isosorbide dinitrate is metabolised to isosorbide 2-mononitrate with a half life of 2.01 h (±0.4 h) to 2.5 h and isosorbide 5-mononitrate with a half-life of 4.6 h (±0.8 h). Both metabolites are pharmacologically active.

The relative bioavailability of Isoket Retard in comparison to the non-sustained-release tablet amounts to more than 80% after oral use.

### 5.3 Preclinical safety data

None stated.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate
Talc
Polyvinyl acetate
Magnesium stearate
Potato starch

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

5 years.

### 6.4 Special precautions for storage

No special precautions

### 6.5 Nature and contents of container

Cartons of blister strips of polypropylene (PP) and aluminium or of PP/PP
Pack sizes 50, 56, 60, 84 and 90 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Norgine Pharmaceuticals Limited
ARC Uxbridge, Building 01,
Sanderson Road,
Uxbridge,
UB8 1DH, UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 20011/0048

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

**Date of first authorisation:** 01 June 1981

**Date of latest renewal:** 30 June 2008

## 10 DATE OF REVISION OF THE TEXT

08/04/2025