SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ISMO Retard, 40 mg, prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 40 mg isosorbide-5-mononitrate.

Excipient with known effect: lactose, sucrose and liquid glucose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Circular, white sugar coated, prolonged-release tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISMO Retard is indicated for the prophylaxis of angina pectoris.

4.2 Posology and method of administration

Posology

Paediatric Population

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

ISMO Retard has been developed to provide a convenient, once daily dosage form of isosorbide-5-mononitrate. It is designed to achieve therapeutic blood concentrations within 30 minutes which persist up to 17 hours. A nitrate free interval of up to 7 hours makes the development of anti-anginal tolerance during chronic therapy unlikely.

The tablets should be taken with fluid and swallowed whole without chewing.

Adults

One tablet daily to be taken in the morning.

Patients who have not previously received nitrates may initially be started with a low dose which should be gradually increased before introducing ISMO Retard. The lowest effective dose should be used.

Therapy should not be discontinued suddenly (see section 4.4).

Elderly

There is no evidence to suggest an adjustment of dose is necessary. However, caution may be required in elderly patients who are known to be susceptible to the effects of hypotensive medication.

Renal and hepatic impairment
No dosage reduction is necessary.

Method of administration
Oral.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- hypersensitivity to isosorbide dinitrate
- in cases of marked low blood pressure (BP ≤ 90 mm Hg systolic)
- circulatory collapse
- shock
- cardiogenic shock
- acute myocardial infarction with low left ventricular filling pressure
- hypertrophic obstructive cardiomyopathy
- constrictive pericarditis
- cardiac tamponade
- aortic/mitral valve stenosis
- severe anaemia
- closed-angle glaucoma and conditions associated with raised intracerebral pressure e.g. following head trauma and cerebral haemorrhage
- severe hypovolaemia
- Phosphodiesterase-5 inhibitors, e.g. sildenafil, vardenafil and tadalafil have been shown to potentiate the hypotensive effects of nitrates (see section 4.8), and their co-administration with nitrates or nitric oxide donors is therefore contraindicated.

4.4 Special warnings and precautions for use

ISM0 Retard is not indicated for relief of acute anginal attacks. In the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets or spray should be used.

Since a rebound phenomenon cannot be excluded, therapy with isosorbide-5-mononitrate should be terminated gradually rather than stopping abruptly (see section 4.2).

Caution should be exercised in patients suffering from hypothyroidism, malnutrition, severe renal or hepatic impairment, hypothermia and recent history of myocardial infarction and in patients already taking medicine to lower blood pressure or taking any other medication (see section 4.5).

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

Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol.

Tolerance development and occurrence of cross-tolerance with other nitrate compounds have been described. In order to avoid any attenuation or loss of effect, high continuous dosing regimens should be avoided.

Administration of isosorbide-5-nitrate may produce transient hypoxaemia as a result of redistribution of blood flow with a relative increase in perfusion of poorly ventilated areas of the lung. This may cause ischaemia in patients with coronary heart disease.

Dose escalation and/or changes in the dosing interval can lead to an attenuation or loss of the effect.

Patients with rare hereditary problems of galactose intolerance or fructose intolerance, the Lapp
lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of other vasodilatators, antihypertensives (e.g. ACE-inhibitors, angiotensin-II-receptor antagonists, beta-blockers, calcium antagonists, diuretics), neuroleptics, sapropterin, alprostadil, aldesleukin and alcohol can potentiate the hypotensive effect of ISMO Retard.

In particular, the hypotensive effects of nitrates are potentiated by concurrent co-administration of phosphodiesterase type-5 inhibitors e.g. sildenafil, vardenafil and tadalafil (see section 4.3); these effects are potentially life threatening.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of safety of isosorbide-5-mononitrate in human pregnancy although nitrates have been in wide use for many years without ill consequence, animal studies having shown no adverse effects on the foetus. Use in pregnancy is not recommended unless considered essential by the patient's physician.

Lactation

There is no information on excretion of isosorbide-5-mononitrate in breast milk.

Use in lactation is not recommended unless considered essential by the patient’s physician.

Fertility

There are no fertility data.

4.7 Effects on ability to drive and use machines

In theory, the ability to drive or to operate machinery may be impaired in patients experiencing hypotensive side effects such as dizziness or blurred vision.

4.8 Undesirable effects

The following categories are used when stating the frequency of undesirable effects:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

Nervous system disorders

- Very common: Particularly at the start of treatment, a transient “nitrate headache” may occur which normally subsides after some days of continued treatment.

Vascular disorders

- Common: Especially at the beginning of treatment, hypotension (including postural hypotension) has been observed which may be accompanied by tachycardia and slight states of
dizziness or feeling of weakness, which normally improves on continuation of therapy.

- **Uncommon:** A significant drop in blood pressure with exacerbation of angina pectoris symptoms has been observed as well as states of collapse, sometimes accompanied by bradyarrhythmias and syncope.
- **Not known:** Severe hypotensive responses including nausea, vomiting, restlessness, pallor, and hyperhidrosis have been reported for organic nitrates.

**Skin and subcutaneous tissue disorders**
- **Uncommon:** flushing
- **Not known:** exfoliative dermatitis

**Immune system disorders**
- **Uncommon:** allergic skin reactions

**Blood and lymphatic system disorders**
- **Not known:** formation of methaemoglobin, in particular in susceptible patients such as those with methaemoglobin reductase deficiency or in patients with diaphorase deficiency and abnormal haemoglobin structure

**Gastro-intestinal disorders**
- **Common:** Especially when first used, gastro-intestinal symptoms, e.g. nausea and/or vomiting may occur.
- **Not known:** heartburn

**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 Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

### 4.9 Overdose

**Symptoms of an overdose**

nausea, vomiting, restlessness, warm flushed skin, blurred vision, headache, fainting, tachycardia, hypotension and palpitations.

At high doses (more than 20 mg/kg body weight), methaemoglobin formation, cyanosis, dyspnoea and tachypnoea can be expected, as a result of the nitrite ion formed when isosorbide-5-mononitrate is degraded.

At very high doses, increased intracranial pressure with cerebral symptoms may occur.

In cases of chronic overdose, increased methaemoglobin levels have been measured, the clinical relevance of which is debated.

**Measures to treat overdose**
In addition to general procedures, such as gastric lavage and keeping the patient horizontal with the legs raised, vital parameters must be monitored under intensive care conditions and corrected where necessary.

In the event of marked hypotension and/or shock, volume replacement should be given; in exceptional cases, norepinephrine and/or dopamine can be infused as circulatory therapy. Administration of epinephrine and related substances is contraindicated.

For methaemoglobinaemia, the following antidote is available:
Methylene blue: Up to 50 ml of a 1 % methylene blue solution IV

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: isosorbide mononitrate, ATC code: C01DA14

The main effect of isosorbide-5-mononitrate is to produce a marked venous vasodilation without a significant effect on the systemic arteries. The venous dilation leads to an accumulation of blood in the capacitance vessels resulting in a reduction of venous return to the heart. This results in a reduction of the ventricular diastolic volume, which produces a reduction in intramural tension (afterload) as well as reductions of filling pressures and pulmonary capillary pressure (preload) and as a result, a reduction in myocardial oxygen requirements from which arises the antianginal effect.

Beta-blocking drugs have a different pharmacological action in angina and may have a complementary effect when co-administered with ISMO Retard.

5.2 Pharmacokinetic properties

Isosorbide-5-mononitrate rapidly and completely absorbed following oral administration. Elimination is by hepatic metabolism to inactive metabolites. The elimination half life is slightly more than 4 hours.

ismo retard releases isosorbide-5-mononitrate over several hours. Therapeutic serum levels are present within 30 minutes of a dose. Peak serum concentrations occur between 3 and 4 hours post administration. Pharmacologically active serum concentrations are maintained for up to 17 hours. Simulation studies indicate that accumulation will not occur in hepatically normal patients.

The drug is eliminated solely by the liver and therefore can be used in renal insufficiency.

Anti-anginal tolerance is unlikely to occur during chronic use as the dosage regime provides up to 7 hours daily when isosorbide-5-mononitrate serum concentration is below pharmacologically active values.

5.3 Preclinical safety data

No special findings.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

ISMO Retard also contains anhydrous lactose, montan glycol wax, povidone K25, colloidal silicone dioxide and magnesium stearate. The tablets are covered by a sugar coating which contains methacrylic acid copolymer, talc, sucrose, kaolin, macrogol 35000, titanium dioxide, povidone K25, liquid glucose and montan glycol wax. No azo dyes are used as colouring substances. (The sugar content of each tablet is less than 36 mg).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Packs of 28 or 30 tablets in blister strips or 28 tablets in HDPE containers.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

RIEMSER Pharma GmbH, An der Wiek 7, 17493 Greifswald - Insel Riems, Germany

8 MARKETING AUTHORITY NUMBER(S)

PL 42336/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2005
10 DATE OF REVISION OF THE TEXT

22/07/2015