SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ISMO 20, 20 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 20 mg isosorbide-5-mononitrate.

Excipient with known effect: lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral use.

White, circular, uncoated tablets marked with a score line and BM 3B on both faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISMO products are indicated for use in the treatment and prophylaxis of angina pectoris and as adjunctive therapy in congestive heart failure which does not respond adequately to cardiac glycosides and/or diuretics.

4.2 Posology and method of administration

Posology

*Paediatric Population*

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

*Adults*

The recommended dosage is from 20 to 120 mg isosorbide-5-mononitrate daily in divided doses. The majority of patients will require a dosage in the range of 40 to 60 mg daily in divided doses. The tablets should be taken with fluid and swallowed whole without chewing.

The lowest effective dose should be used.

For patients who have not previously received prophylactic nitrate therapy it is recommended that the ISMO Starter Pack be employed. This provides an initial dosage of 10 mg isosorbide-5-mononitrate (1 tablet) daily for 2 days followed by a dosage of 20 mg daily (1 tablet morning and evening) for a further 3 days. Subsequently the daily dosage may be increased to the normal prophylactic level using the ISMO 20 tablets also included in the Starter Pack. Patients already accustomed to chronic nitrate therapy normally may be transferred directly to a therapeutic dose of ISMO.

For those previously treated with isosorbide dinitrate in conventional form the dosage of ISMO should be the same initially. ISMO is effectively twice as potent as sustained release forms of isosorbide.
dinitrate and patients transferred from such treatment should receive ISMO at half the previous dosage.

Therapy should not be discontinued suddenly. Both dosage and frequency should be tapered gradually (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 \(\leq 90\) 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

ISMO is not indicated for relief of an acute attack; sublingual or buccal glyceryl trinitrate tablets or spray should be used.

The lowest effective dose should be used (see section 4.2).

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, the Lapp lactase deficiency or glucose-galactose malabsorption 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 20.

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

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

**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.

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
Management: 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

ISMO provides long-term nitrate treatment of angina pectoris and heart failure in a form with complete biological availability due to lack of any significant hepatic first-pass metabolism. This provides consistently uniform blood levels of drug substance and a predictable clinical response. The onset of activity occurs within 20 minutes, and, depending on dosage, is maintained for up to 10 hours.

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

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 (preload) and as a result, a reduction in myocardial oxygen requirements from which arises the antianginal effect.

5.2 Pharmacokinetic properties

Isosorbide-5-mononitrate displays 100% bioavailability on oral administration. Consequently, serum levels are predictable. Isosorbide-5-mononitrate is rapidly absorbed - peak serum concentrations occurring 1 hour after oral administration. Elimination half life is approximately 5 hours.

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

5.3 Preclinical safety data

No special findings.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
ISMO 20 tablets also contain anhydrous lactose, colloidal silicon dioxide and magnesium stearate.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
5 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
ISMO Starter Pack: 8 tablets of ISMO 10 and 56 or 60 tablets of ISMO 20 in calendarised blister strips.

ISMO 20: Packs of 56, 60 and 100 tablets in blister strips or 100, 250 or 500 tablets in Securitainers.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Riemser Pharma GmBH
An Der Wiek 7
Greifswald
D-17493
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 42336/0004

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26/05/2005
10 DATE OF REVISION OF THE TEXT

22/07/2015