AUSTRALIAN PRODUCT INFORMATION
APO- ISOSORBIDE MONONITRATE (ISOSORBIDE MONONITRATE) SUSTAINED RELEASE TABLETS

1 NAME OF THE MEDICINE

Isosorbide mononitrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

APO- Isosorbide Mononitrate Sustained Release Tablets contain 60 mg isosorbide mononitrate.

Excipients with known effect

Lactose monohydrate

For the full list of excipients see section 6.1 **List of Excipients**

3 PHARMACEUTICAL FORM

APO- Isosorbide Mononitrate 60 mg Sustained Release Tablets:

A cream, film-coated oval tablet of 13mm length, half scored on both sides.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prophylactic treatment of angina pectoris. APO- Isosorbide Mononitrate 60 mg Sustained Release Tablets are not recommended for the management of acute attacks of angina pectoris (see section **4.4 Special warnings and precautions for use**).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

One (1) tablet once daily. That dose may be increased to two (2) tablets daily, both tablets taken at the same time.

APO- Isosorbide Mononitrate 60 mg Sustained Release Tablets should not be administered twice daily.

There is insufficient evidence to show that one halved tablet of APO- Isosorbide Mononitrate delivers exactly half the dose of one full tablet, or whether the rate of release is the same. *In-vitro* dissolution testing showed that dissolution was slightly faster with halved APO- Isosorbide Mononitrate Sustained Release Tablets than with whole tablets.

APO- Isosorbide Mononitrate 60 mg Sustained Release Tablets should not be chewed or crushed, and should be swallowed whole with half a glass of fluid.

4.3 CONTRAINDICATIONS

- Known hypersensitivity to nitrates or to any of the components in APO- Isosorbide Mononitrate 60 mg Sustained Release Tablets.
- Shock (including cardiogenic shock), hypotension, obstructive hypertrophic cardiomyopathy and pericarditis, aortic stenosis, cardiac tamponade, mitral stenosis and severe anaemia.

- **Phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) are contraindicated and must not be given to patients already receiving isosorbide mononitrate therapy.**

  Concomitant administration of isosorbide mononitrate and Phosphodiesterase type 5 inhibitors can potentiate the vasodilatory effect of isosorbide mononitrate with the potential result of serious side-effects such as syncope or myocardial infarction.

- Severe cerebrovascular insufficiency or hypotension are relative contraindications to the use of Isosorbide Mononitrate 60 mg Sustained Release Tablets.

- **Acute Angina**
  Isosorbide Mononitrate 60 mg Sustained Release Tablets are not indicated for the relief of acute attacks of angina; in the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets should be used.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Note : There is a risk of developing tolerance to haemodynamic and antianginal effects if higher doses (more than 120 mg/day) and/or more frequent doses (e.g. twice daily) of Isosorbide Mononitrate 60 mg Sustained Release tablets are administered. It is therefore important that Isosorbide Mononitrate 60 mg Sustained Release Tablets are administered once a day in order to ensure that intervals with low nitrate concentrations are achieved each day, reducing the risk of the development of tolerance.

Cerebral Arteriosclerosis or Mitral Stenosis

Caution should be observed if isosorbide mononitrate is administered to patients with severe cerebral arteriosclerosis or pronounced mitral stenosis.

Acute Myocardial Infarction and Congestive Cardiac Failure

The benefits of isosorbide mononitrate in patients with acute myocardial infarction or congestive cardiac failure have not been established. Because the effects of isosorbide mononitrate are difficult to terminate rapidly, the medicine is not recommended in these settings. If isosorbide mononitrate is used in these conditions, careful clinical and haemodynamic monitoring is necessary to avoid the hazards of hypotension and tachycardia.

Hypotension

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide mononitrate. Hypotension and lightheadedness on standing may be more frequent in patients who have consumed alcohol. The drug should be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Industrial Workers

Tolerance develops in industrial workers who have had long-term exposure to high doses of organic nitrates. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Check the Following Before Use

Caution should be observed Isosorbide Mononitrate 60 mg Sustained Release Tablets are administered to patients with: severe cerebral arteriosclerosis, pronounced mitral stenosis, hypertrophic cardiomyopathy, hypotension or cardiogenic shock.

Use with Caution in the Following Circumstances

Use in renal impairment

The elimination of isosorbide mononitrate following administration of an immediate release tablet but not a sustained release tablet, has been investigated in patients with severe renal impairment, but not using the sustained release tablet. Renal impairment makes no therapeutically important difference to the pharmacokinetics of isosorbide mononitrate administered as an immediate release tablet, although two single dose studies did indicate a prolonged half-life in these patients with severe renal impairment. One of these studies also showed a higher plasma concentration. In view of the lack of data regarding the use of the tablet presentation in patients with severe renal impairment, the possibility of accumulation should be borne in mind when administering Isosorbide Mononitrate 60 mg Sustained Release Tablets to such patients, in whom a reduced dosage may be appropriate.

Use in hepatic impairment

Isosorbide mononitrate has been shown to cause a significant decrease in portal pressure in patients with cirrhosis and portal hypertension during long-term therapy (see section **4.5 Interactions with other medicines and other forms of interactions – Propranolol**).

Abrupt Withdrawal

Although no clear cut rebound phenomena were seen upon abrupt withdrawal of isosorbide mononitrate sustained release tablets, such withdrawal is not recommended because of the possibility of severe exacerbation of anginal symptoms.

Paediatric use

Due to lack of data, the use of Isosorbide Mononitrate 60 mg Sustained Release Tablets cannot be recommended in children.

Use in the elderly

No dose reduction is necessary in elderly patients unless they have severe renal impairment.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Phosphodiesterase Type 5 Inhibitors

Concomitant administration of isosorbide mononitrate and Phosphodiesterase Type 5 inhibitors can potentiate the vasodilatory effect of isosorbide mononitrate with the potential result of serious side-effects such as syncope or myocardial infarction. Therefore, Phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) must not be given to patients already receiving isosorbide mononitrate therapy.

Sulfhydryl Containing Compounds

The metabolism of organic nitrates to nitric oxide is dependent on the presence of sulfhydryl groups in the muscle. The combination of oral N-acetylcysteine and a single dose of sustained release isosorbide mononitrate 60 mg significantly prolonged the total exercise time in patients with angina pectoris and angiographically proven significant coronary artery disease, when compared with isosorbide mononitrate alone. Concomitant administration of other exogenous sources of sulfhydryl groups such as methionine and captopril may produce a similar interaction.

Phenylalkylamine Calcium Antagonists

The addition of a calcium channel blocker of the verapamil type, such as gallopamil 75 mg, has been shown to further improve left ventricular functional parameters when given in combination with isosorbide mononitrate in a sustained release formulation.

Propranolol

The addition of isosorbide mononitrate to propranolol treatment in patients with cirrhosis and portal hypertension caused a marked fall in portal pressure, a reduction in hepatic blood flow, cardiac output and mean arterial blood pressure, but no additional change in azygos blood flow. The additional effect of isosorbide mononitrate was especially evident in patients whose portal pressure was not reduced by propranolol.

Calcium Antagonists (General)

Marked symptomatic orthostatic hypotension has been reported when calcium antagonists and organic nitrates were used in combination. Dose adjustments of either class of agent may be necessary.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category B2

The safety of isosorbide mononitrate in pregnancy has not been established. In the absence of Segment I and III studies with isosorbide mononitrate, the drug should only be administered to pregnant women if, in the opinion of the physician, the clinical benefits outweigh the potential risks.

Use in lactation

At present there is no documentation about the passage of isosorbide mononitrate into breast milk, therefore its use in women who are breastfeeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients may develop dizziness when first using isosorbide mononitrate. Patients should be advised to determine how they react before they drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects associated with the vascular activity of the drug are common and as expected with all nitrate preparations. They occur mainly in the early stages of treatment. Headache predominates (up to 30%), but the incidence reduces rapidly as treatment continues. Only 2-3% of patients withdrew during clinical trials due to this adverse effect.

Hypotension (4%) with symptoms such as dizziness and nausea have been reported. These symptoms generally disappear during long-term treatment.

The adverse reactions which follow have been reported in studies with isosorbide mononitrate:

Very Common	Headache (up to 30%) necessitating withdrawal of 2-3 % of patients.

Common	Tiredness, sleep disturbances (6%) and gastrointestinal disturbances (6%) have been reported during clinical trials with isosorbide mononitrate modified release tablets, but at a frequency no greater than for placebo. Hypotension (4 to 5%), poor appetite (2.5%), nausea (1%).

Adverse effects associated with the clinical use of the drug are as expected with all nitrate preparations. They occur mainly in the early stages of treatment:

Very Common	Headache predominates (up to 30%), but the incidence reduces rapidly as treatment continues.
Common	Hypotension (4%) with symptoms such as dizziness and nausea have been reported. These symptoms generally disappear during long-term treatment.

Other reactions that have been reported with isosorbide mononitrate modified release tablets include: tachycardia, vomiting, diarrhoea, vertigo, fainting, poor appetite, nausea, heartburn, rash and pruritus.

The following adverse events have been observed in the post-marketing period (definitions of frequency: common 1 - 9.9%; uncommon 0.1 - 0.9%; rare 0.01 - 0.09%; very rare < 0.01%).

Central nervous system	Common: dizziness
Musculoskeletal	Very rare: Myalgia

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Symptoms

The most common symptom of overdose is a pulsing headache. More serious symptoms are excitation, flushing, cold sweats, nausea, vomiting, vertigo, syncope, tachycardia and a fall in blood pressure.

Treatment

Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. In patients with severe hypotension, place patient in supine position with the legs raised. If necessary, further symptomatic treatment should be given, including intravenous fluid administration.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Isosorbide mononitrate is an active metabolite of isosorbide dinitrate and exerts qualitatively similar effects. Isosorbide mononitrate reduces the workload of the heart by producing venous and arterial dilatation. By reducing the end diastolic pressure and volume, isosorbide mononitrate lowers intramural pressure, hence leading to an improvement in the sub-endocardial blood flow. The net effect when administering isosorbide mononitrate is therefore a reduced workload for the heart and an improvement in the oxygen supply/demand balance of myocardium.

Nitrates are highly effective in the prophylaxis of symptomatic and asymptomatic myocardial ischaemia. Nitrates dilate coronary arteries not only in pre- and post-stenotic vessels, but also in eccentric lesions. The natural initiator of vascular relaxation is thought to be endothelium derived relaxing factor (EDRF), which has both the clinical and biological characteristics of nitric oxide. Organic nitrates are metabolised to nitric oxide in the muscle cell via a sulfhydryl dependent mechanism. They are therefore thought to be the physiological substitute for EDRF.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Isosorbide mononitrate has an elimination half-life of around 5 hours. Isosorbide Mononitrate 60 mg Sustained Release Tablets provide a sustained release presentation of isosorbide mononitrate, with approximately 85% bioavailability. The release mechanism in APO- Isosorbide Mononitrate comprises active drug distributed within a hydrophobic cellulose matrix with release occurring by diffusion. Drug particles close to the tablet surface are released relatively rapidly, but those incorporated more deeply are released more slowly. Administration of Isosorbide Mononitrate 60 mg Sustained Release Tablets results in a gradual, non-pH dependent release of the active substance, which is completed after approximately 10 hours. Compared to ordinary tablets, the absorption phase is prolonged and the duration of effect is extended. The absorption of Isosorbide Mononitrate 60 mg Sustained Release Tablets has been shown not to be influenced by food intake.

After repeated once daily administration of Isosorbide Mononitrate 60 mg Sustained Release Tablets, the maximum plasma level (about 3000 nmol/L) of isosorbide mononitrate is achieved at about 4 hours. The plasma concentration remains above 1400 to 1500 nmol/L for approximately 10 hours, dropping to under 500 nmol/L by the end of the dosage interval (24 hours after dose). This nitrate low period minimises the possibility of nitrate tolerances developing during prolonged treatment with Isosorbide Mononitrate 60 mg Sustained Release Tablets.

Isosorbide mononitrate is less than 5% plasma protein bound. The distribution volume of isosorbide mononitrate is about 0.6 L/kg, indicating that it is mainly distributed into total body water. Elimination takes place predominantly by hydrolysis of the nitrate and conjugation in the liver. The metabolites are excreted mainly via the kidneys, with only about 2% of the dose being excreted intact.

In placebo controlled studies, isosorbide mononitrate sustained release tablets have been shown to significantly increase exercise capacity in patients with angina pectoris taking no other chronic treatment, as well as in patients taking concomitant β-blocker therapy.

It is known that the clinical effects may be attenuated during repeated administration with nitrates in high doses and/or frequent administration. However, the pharmacokinetic characteristics of

Isosorbide Mononitrate 60 mg Sustained Release Tablets produce a nitrate low period following once daily dosage. No development of tolerance with respect to antianginal effect has been detected when Isosorbide Mononitrate Sustained Release Tablets are given at a dose of one or two tablets (60 or 120 mg) once daily. The drug is not recommended for twice daily administration.

There is insufficient evidence to show that one halved tablet of APO- Isosorbide Mononitrate delivers exactly half the dose of one full tablet, or whether the rate of release is the same. *In-vitro* dissolution testing showed that dissolution was slightly faster with halved isosorbide mononitrate sustained release tablets than with whole tablets.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Hypromellose
- carnauba wax
- stearic acid
- lactose monohydrate
- purified siliceous earth
- magnesium stearate
- purified talc
- titanium dioxide
- iron oxide yellow C177492
- macrogol

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 degrees. Protect from moisture. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

APO- Isosorbide Mononitrate 60 mg Sustained Release Tablets:

30's. AUST R 75240.

APO- is a registered trade mark of Apotex Pty Ltd.

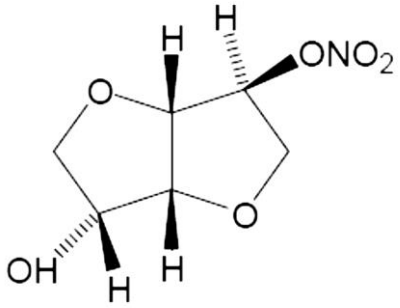
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Isosorbide mononitrate is a white to pale yellow, crystalline, odourless powder that is freely soluble in water.

Chemical structure



Chemical Name: 1,4:3,6-dianhydro-D-glucitol 5-nitrate.

Molecular Formula: $C_6H_9NO_6$

Molecular Weight: 191.14

CAS number: 16051-77-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

25 August 2000

10 DATE OF REVISION

14 February 2019

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information; minor editorial changes
All	Changed trade name from GenRx to APO-.
4.5, Interactions With Other Medicines And Other Forms Of Interactions	Spelling error. Corrected lower case to upper case: Phopsphodiesterase to Phosphodiesterease.
6.1	Change of excipient name from: - lactose to lactose monohydrate and - siliceous earth to purified siliceous earth to comply with the new Australian Approved Names (AAN) in accordance with International Harmonisation of Ingredient Names (IHIN).
10	Deleted date of last revision. It will be replaced with the date of approval of the revised PI.