SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Monomil XL Tablets
Carmil XL Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isosorbide – 5 – mononitrate: 60mg/tablet. Also contains lactose.
For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prophylaxis of angina pectoris.

4.2 Posology and Method of Administration

Adults: One tablet to be taken once daily in the morning. The dose may be increased to 120mg (two tablets) daily, both to be taken once daily in the morning. The dose can be titrated to minimise the possibility of headache, by initiating the treatment with 30mg (half tablet) for the first 2 – 4 days.

Monomil XL/Carmil XL tablets must not be chewed or crushed. They should be swallowed whole with a small amount of water.

Children: The safety and efficacy of Monomil XL/Carmil XL tablets in children has not been established.

Elderly: No evidence of a need for routine dosage adjustment in the elderly has been found, but special care may be needed in those with increased susceptibility to hypotension or marked hepatic or renal insufficiency.

4.3 Contraindications
Severe cerebrovascular insufficiency or hypotension are relative contraindications to the use of Monomil XL/Carmil XL tablets.

Monomil XL/Carmil XL tablets should not be given to patients with a known sensitivity to nitrates (or any other ingredient in this product), very low blood pressure, acute myocardial infarction with low filling pressure, acute circulatory failure (shock, vascular collapse), hypertrophic cardiomyopathy and constrictive pericarditis, aortic stenosis, cardiac tamponade, mitral stenosis, severe anaemia and during the first three months of pregnancy.

Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil and vardenafil) have been shown to potentiate the hypotensive effects of nitrates, and their co-administration with nitrates or nitric oxide donors is therefore contraindicated (see section 4.5).

Monomil XL/Carmil XL is contraindicated in diseases associated with a raised intra-cranial pressure e.g. following a head trauma and including a cerebral haemorrhage, and in patients with closed angle glaucoma.

**4.4 Special Warnings and Precautions for use**

Monomil XL/Carmil XL tablets are not indicated for the relief of acute angina attacks; in the event of an acute attack, sublingual or buccal glyceryl trinitrate tablets should be used.

Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol. Consumption of alcohol should be avoided during the treatment with Carmil/Monomil XL tablets as the vasodilator activity of isosorbide mononitrate may be enhanced.

Monomil XL/ Carmil XL tablets should be used with caution in patients who have a recent history of myocardial infarction, or who are suffering from hypothyroidism, hypothermia, malnutrition and severe liver or renal disease.

Monomil XL/Carmil XL tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

**4.5. Interaction with other Medicinal Products and other forms of Interaction**

Concomitant administration of Monomil XL/Carmil XL tablets and Phosphodiesterase Type 5 Inhibitors can potentiate the vasodilatory effect of Monomil XL/Carmil XL tablets with the potential result of serious side effects such as syncope or myocardial infarction. Therefore, Monomil XL/Carmil XL tablets and Phosphodiesterase Type 5 Inhibitors (e.g. sildenafil) must not be given concomitantly.

Concurrent administration of drugs with blood pressure lowering properties, e.g. beta-blockers, calcium channel blockers, vasodilators, alprostadil, aldesleukin, angiotensin II receptor antagonists etc and/or alcohol may
potentiate the hypotensive effect of Monomil XL / Carmil XL. This may also occur with neuroleptics and tricyclic antidepressants.

4.6 **Fertility, pregnancy and lactation**

The safety and efficacy of Monomil XL/Carmil XL tablets during pregnancy or lactation has not been established.

4.7. **Effects on Ability to Drive and Use Machines**

Patients may develop dizziness when first using Monomil XL/Carmil XL tablets. Patients should be advised to determine how they react to Monomil XL/Carmil XL tablets before they drive or operate machinery.

4.8. **Undesirable effects**

The adverse reactions which follow have been reported in studies with isosorbide mononitrate. Most of the adverse reactions are pharmacodynamically mediated and dose dependent.

Headache may occur when treatment is initiated, but usually disappears after 1-2 weeks of treatment. Hypotension, with symptoms such as dizziness and nausea with syncope in isolated cases, has occasionally been reported. These symptoms generally disappear during continued treatment.

The following definitions of frequencies are used: 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) and very rare (<1/10,000).

**Nervous system disorders**

Common: Headache, Dizziness
Rare: Fainting.

**Cardiac disorders**

Common: Tachycardia
Not known: paradoxical bradycardia.

**Vascular disorders**

Common: Postural hypotension, Hypotension
Uncommon: Flushing

**Gastrointestinal disorders**

Common: Nausea
Uncommon: Vomiting, Diarrhoea.

**Skin and subcutaneous tissue disorders**

Rare: Rash and pruritus
Musculoskeletal, connective tissue and bone disorders
Very rare: Myalgia

General disorders and administration site conditions
Not known: Fatigue

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal products 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 at: www.mhra.gov.uk/yellowcard.

4.9- Overdose

Symptoms: Pulsing headache. More serious symptoms are excitation, flushing, cold perspiration, nausea, vomiting, vertigo, syncope, tachycardia and a fall in blood pressure.

Treatment: Induction of emesis, activated charcoal. In case of pronounced hypotension the patient should first be placed in the supine position with the legs raised. If necessary fluids should be administered intravenously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties


The principal pharmacological action of isosorbide mononitrate, an active metabolite of isosorbide dinitrate, is relaxation of vascular smooth muscle, producing vasodilation of both arteries and veins with the latter effect predominating. The effect of the treatment is dependent on the dose. Low plasma concentrations lead to venous dilatation, resulting in peripheral pooling of blood, decreased venous return and reduction in left ventricular end-diastolic pressure (preload). High plasma concentrations also dilate the arteries reducing systemic vascular resistance and arterial pressure leading to a reduction in cardiac afterload. Isosorbide mononitrate may also have a direct dilatory effect on the coronary arteries. By reducing the end diastolic pressure and volume, the preparation lowers the intramural pressure, thereby leading to an improvement in the subendocardial blood flow.
The net effect when administering isosorbide mononitrate is therefore a reduced workload of the heart and an improved oxygen supply/demand balance in the myocardium.

Monomil XL/Carmil XL tablets are effective as monotherapy as well as in combination with beta-blocker therapy.

The clinical effects of nitrates may be attenuated during repeated administration owing to high and/or even plasma levels. This can be avoided by allowing low plasma levels for a certain period of the dosage interval. Extended release tablets containing isosorbide mononitrate, when administered once daily in the morning, produce a plasma profile of high levels during the day and low levels during the night. With the 60mg or 120mg once daily tablet, no development of tolerance with respect to antianginal effect has been observed. Rebound phenomenon between doses as described with intermittent nitrate patch therapy has not been seen with this formulation.

In placebo-controlled studies, once daily extended release tablets containing isosorbide mononitrate have been shown to effectively control angina pectoris both in terms of exercise capacity and symptoms, and also in reducing signs of myocardial ischaemia. The duration of the effect is at least 12 hours; at this point the plasma concentration is at the same level as at around 1 hour after dose intake (around 1300 nmol/l).

5.2 Pharmacokinetics properties

Absorption
Isosorbide mononitrate is completely absorbed and is not subject to first pass metabolism by the liver. This reduces the intra- and inter-individual variations in plasma levels and leads to predictable and reproducible clinical effects. Monomil XL/Carmil XL Tablets are prolonged release formulations. The active substance is released independently of pH, over a 10-hour period. Compared to ordinary tablets the absorption phase is prolonged and the duration of effect is extended.

The extent of bioavailability of isosorbide mononitrate in extended release tablets is about 90% compared to immediate release tablets. Absorption is not significantly affected by food intake and there is no accumulation during steady state.

Isosorbide mononitrate in extended release tablets exhibits dose proportional kinetics up to 120mg. After repeated peroral administration with 60mg once daily, maximal plasma concentration (around 3000 nmol/l) is achieved after around 4 hours. The plasma concentration then gradually falls to under 500 nmol/l at the end of the dosage interval (24 hours after dose intake).

Distribution
The plasma protein binding is less than 5%. The volume of distribution for isosorbide mononitrate is about 0.6 l/kg and total clearance around 115 ml/minute.
Elimination
Elimination is primarily by denitration and conjugation in the liver. The metabolites are excreted mainly via the kidneys. Only about 2% of the dose given is excreted intact via the kidneys.

The elimination half-life of isosorbide mononitrate is around 5 hours.

Impaired liver or kidney function has no major influence on the pharmacokinetic properties.

5.3- Preclinical safety data
Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate, hypromellose, maize starch, glyceryl palmitostearate and magnesium stearate.

6.2 Incompatibilities
None known.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C. Store in original container.

6.5 Nature and contents of container
PVC/Aluminium blisters in a cardboard carton. Each strip of blister contains 14 tablets and there are two strips of blisters per carton.
6.6 **Instructions for use/handling**

Not applicable.

7. **MARKETING AUTHORISATION HOLDER**
Milpharm Limited
Ares, Odyssey Business Park
West End Road
South Ruislip, HA4 6QD
United Kingdom

8. **MARKETING AUTHORISATION NUMBER**

PL 16363/0003

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

12/05/2005

10. **DATE OF REVISION OF THE TEXT**

20/01/2016