Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cardioplast 0.2mg/h transdermal patches

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Glyceryl trinitrate

Each Cardioplast 0.2mg/h transdermal patch contains 20.7 mg of glyceryl trinitrate in a patch size of 7.4 cm^2, releasing 0.2 mg of glyceryl trinitrate per hour (4.8 mg/24 h).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal Patch

A translucent rectangular patch with rounded corners, marked with “Glyceryl trinitrate” and the release rate. The following is printed on each patch:
“Glyceryl trinitrate 0.2 mg/h (5mg/24 h)”

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For prophylaxis of angina pectoris either alone or in combination with other anti-anginal therapy.

4.2 Posology and method of administration

Posology
Adults including elderly patients:

Cardioplast transdermal patch it is not indicated for the immediate treatment of an acute anginal attacks. If anginal attacks occur, rapid-acting nitrate preparations (like spray) should be used.

In order to avoid an attenuation of effect, in patients being treated with sustained release nitrate preparations, intermittent therapy is recommended.

The recommended initial dose is one Cardioplast 0.2 mg/h equivalent to 5 mg/24 h patch applied to the skin once daily for a period of approximately 12 hours. The patch is then removed to provide a nitrate-free interval of at least 8 hours which may be increased up to 12 hours to suit individual patients (a daily patch-off period of 8-12 hours).

In case of insufficient efficacy, the posology can be progressively increased to one Cardioplast 0.4 mg/h equivalent to 10 mg/24 h patch once daily, and if necessary to a maximum of one Cardioplast 0.6 mg/h equivalent to 15 mg/24 h patch daily.

Maximum dose is one Cardioplast 0.6 mg/h patch in each 24 hour period (15mg/24 h).

The nitrate-free interval should correspond to a time period when patient does not usually experience crises, and should be covered by another anti-anginal treatment (beta-blocker or calcium channel blocker). This may be especially of relevance in patients with severe angina.
Prescribers should clearly mention on the prescription the hours of application and removal of the patch.

Continuous administration may exceptionally be appropriate for patients in whom clinical responsiveness can be

reliably assessed.

Patients experiencing nocturnal angina may benefit from overnight treatment with a nitrate-free interval during the day. In this patient group additional anti-anginal therapy may be needed during the day.

Paediatric patients:
Safety and efficacy of glyceryl trinitrate have not been established in children and adolescents. Therefore, the use of glyceryl trinitrate is not recommended in these populations.

Method of administration
Cardioplast transdermal patches may be applied to any convenient skin area; the recommended site is the chest or outer upper arm. Application sites should be rotated and hair on suitable areas may beif necessary clipped as close to the skin as possible but not shaved.
Cardioplast transdermal patches should not be applied to the distal part of the extremities.

Instructions for use
Cardioplast transdermal patches are applied only to intact skin after removal from protective sachet. The clear peelable liner on the adhesive side of the patch has a slit which divides it into two strips. Hold the patch with the wording away from the user and with the slit facing the user. Bend the edges away to break open the clear liner. The halves of the cover are peeled off, being careful not to touch the sticky side of the patch, and the patch applied firmly to the skin. Hands should be washed thoroughly after application.

Patients should be advised to dispose of patches carefully to avoid accidental application or use.

4.3 Contraindications

- Hypersensitivity to the active substance, related organic nitrates or to any of the excipients listed in section 6.1
- Marked anaemia
- Acute circulatory failure associated with marked hypotension (shock)
- Severe hypotension (systolic blood pressure less than 90 mmHg)
- Severe hypovolaemia
- Conditions associated with elevated intracranial pressure e.g. cerebral haemorrhage, head trauma
- Myocardial insufficiency due to obstruction, as in aortic or mitral stenosis or left ventricular outflow obstruction, hypertrophic obstructive cardiomyopathy, cardiac tamponade, constrictive pericarditis
- Closed-angle glaucoma

Concomitant use of Cardioplast transdermal patches and phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil, tadalafil, vardenafil are contraindicated, because PDE5 inhibitors may amplify the vasodilatory effects of Cardioplast resulting in severe hypotension.

4.4 Special warnings and precautions for use

Cardioplast is not indicated for the immediate treatment of acute anginal attacks.

As with other nitrate preparations, when transferring the patient on long-term therapy to another form of medication, glyceryl trinitrate should be gradually withdrawn and overlapping treatment started.

Cardioplast transdermal patch must be removed before applying magnetic or electrical fields to the body during procedures such as MRI (Magnetic Resonance Imaging), cardioversion or DC defibrillation, or diathermy treatment.

Caution should be exercised in patients suffering from hypothyroidism, malnutrition, severe renal or hepatic impairment, hypothermia and recent history of myocardial infarction.

In cases of recent myocardial infarction or acute or congestive heart failure, treatment with Cardioplast transdermal patch should be carried out cautiously under strict medical surveillance and/or haemodynamic monitoring.

In some patients severe hypotension may occur particularly with upright posture, even with small doses of glyceryl trinitrate. Thus Cardioplast should be used with caution in patients who may have volume depletion from diuretic therapy and in patients who have low systolic blood pressure. See also section 4.3

Paradoxical bradycardia and increased angina may accompany glyceryl-trinitrate-induced hypotension.

Removal of the patch should be considered as part of the management of patients who develop significant hypotension.

Severe postural hypotension with light-headedness and dizziness is frequently observed after the consumption of alcohol by patients being treated with glyceryl trinitrate.

Hypoxaemia:
Caution should be exercised in patients with arterial hypoxaemia due to severe anaemia (including G6PD deficiency induced forms), because in such patients the biotransformation of glyceryl trinitrate is reduced. Similarly, caution is called for in patients with hypoxaemia and ventilation/perfusion imbalance due to lung disease or ischaemic heart failure. In patients with alveolar hypoventilation a vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung (Euler-Liljestrand mechanism).Patients with angina pectoris, myocardial infarction, or cerebral ischaemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, glyceryl trinitrate could reverse this protective vasoconstriction and thus 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.

Hypertrophic cardiomyopathy:
Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Increased angina:
The possibility of increased frequency of angina during patch-off periods should be considered. In such cases the use of concomitant anti-anginal therapy is desirable.

Tolerance to sublingual glyceryl trinitrate:
As tolerance to glyceryl trinitrate patches develops, the effect of sublingual glyceryl trinitrate on exercise tolerance may be partially diminished.

This product should be used with extreme caution in patients pre-disposed to closed angle glaucoma.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a concomitant use contraindicated:
Concomitant administration of Cardioplast transdermal patch and other vasodilators (e.g. PDE5 inhibitors such as sildenafil, tadalafil, vardenafil potentiates the blood-pressure-lowering effect of Cardioplast transdermal patch.

Interactions to be considered:
Concomitant treatment with calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants and major tranquillisers may potentiate the blood-pressure-lowering effect of Cardioplast transdermal patch, as may alcohol.

Concurrent administration of Cardioplast transdermal patch with dihydroergotamine may increase the bioavailability of dihydroergotamine. This warrants special attention in patients with coronary artery disease, because dihydroergotamine antagonises the effect of glyceryl trinitrate and may lead to coronary vasoconstriction.

Non-steroidal anti-inflammatory drugs, with the exception of acetyl salicylic acid, may diminish the therapeutic response of Cardioplast transdermal patch.

Concurrent administration of Cardioplast transdermal patch with amifostine and acetyl salicylic acid may potentiate the blood pressure lowering effects of Cardioplast transdermal patch.

4.6 Fertility, pregnancy and lactation

Fertility
There is no data available on the effect of Cardioplast transdermal patch on fertility in humans. Animal data do not indicate a risk of adverse effects on fertility.

Pregnancy
Results from animal reproductive toxicity studies do not indicate a risk of adverse effects on embryo-foetal development. It is not known whether glyceryl trinitrate in transdermal form can affect reproductive capacity or cause foetal harm in humans. Thus Cardioplast should only be administered to pregnant women if the potential benefit to the mother clearly outweighs the potential hazard to the foetus. Caution should be advised during the first trimester of pregnancy.

Breast-feeding
It is not known whether glyceryl trinitrate is excreted in human milk. Caution should therefore be exercised when Cardioplast is administered to nursing mothers.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Cardioplast transdermal patch therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Cardioplast transdermal patch has moderate influence on the ability to drive and use machines.
Especially at the start of treatment or dose adjustments, Cardioplast transdermal patch may impair the reactions or might rarely cause orthostatic hypotension and dizziness (as well as exceptionally syncope after overdosing). Patients experiencing these effects should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions are listed by MedDRA System-Organ Class (SOC). Within each System-Organ Class the adverse drug reactions are ranked by frequency, with the most frequent first. Within each frequency grouping, adverse drug reactions are ranked in order of decreasing seriousness. In addition, the corresponding frequency category, using the following convention (CIOMS III): Very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Nervous system disorders		Headache[1]			Dizziness	
Cardiac disorders				Tachycardia[2]		Palpitation[4]
Vascular disorders				Orthostatic hypotension, Flushing[2]		
Gastrointestinal disorders	Nausea, Vomiting					
Skin and subcutaneous tissue disorders			Contact dermatitis			Rash generalised[4]

General disorders and administration site conditions			Application site erythema, Pruritus, Burning, Irritation[3]			
Investigations				Heart rate increase		

[1] Like other nitrate preparations, Cardioplast transdermal patch commonly causes dose-dependent headaches due to cerebral vasodilatation. These often regress after a few days despite the maintenance of therapy. If headaches persist during intermittent therapy, they should be treated with mild analgesics. Unresponsive headaches are an indication for reducing the dosage of glyceryl trinitrate or discontinuing treatment.

[2]A slight reflex-induced increase in heart rate can be avoided by resorting, if necessary, to combined treatment with a beta-blocker.

[3]Upon removal of the patch, any slight reddening of the skin will usually disappear within a few hours. The application site should be changed regularly to prevent local irritation.

[4]The adverse drug reactions have been derived from post-marketing experience with Cardioplast via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

4.9 Overdose

Signs
High doses of glyceryl trinitrate may lead to severe hypotension and reflex tachycardia or to collapse and syncope. Methaemoglobinaemia has also been reported following accidental overdosage.

Management
The nitrate effect of Cardioplast can be rapidly terminated by removal of the patch or reduction of dose, depending on severity.
Thorough scrubbing of underlying skin may reduce absorption more quickly after removal. Intravenous infusion of normal saline or similar fluid may be necessary to increase the central fluid volume. Any fall in blood pressure or signs of collapse that may occur may be managed by general supportive or resuscitative measures. These include elevation, or if necessary, compression bandaging of the patient’s legs. Adrenaline and related products are ineffective in reversing the severe hypotensive events associated with overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasodilators used in cardiac disease, ATC code: C01D A02.

Glyceryl trinitrate, (as other organic nitrates), is a potent dilator of vascular smooth muscle. The effect on veins predominates over that on arteries resulting in decreased cardiac preload. Systemic vascular resistance is relatively unaffected, heart rate is unchanged or slightly increased and pulmonary vascular resistance is consistently reduced.

In normal individuals or those with coronary artery disease (in the absence of heart failure)
glyceryl trinitrate decreases cardiac output slightly. Doses which do not alter systemic arterial pressure often produce arteriolar dilatation in the face and neck resulting in flushing. Dilatation of the meningeal arterioles may explain the headache which is often reported. Rapid administration of high doses of glyceryl trinitrate decreases blood pressure and cardiac output resulting in pallor, weakness, dizziness and activation of compensatory sympathetic reflexes. A marked hypotensive effect may occasionally occur especially in the upright position.

5.2 Pharmacokinetic properties

Glyceryl trinitrate is rapidly hydrolysed by liver enzymes which are a major factor in bioavailability. Orally administered glyceryl trinitrate is ineffective as a therapeutic agent due to first-pass metabolism and administration has therefore routinely been via the sub-lingual route thus bypassing the hepatic circulation initially. Peak concentrations of glyceryl trinitrate following sub-lingual administration occur within 4 minutes in man with a half-life of 1 to 3 minutes. Transdermal delivery systems provide an alternative route to bypass the hepatic circulation with longer term gradual absorption providing prophylactic dosing. Steady state plasma concentrations of approximately 200 pg/ml are achieved within approximately 2 hours of application of Cardioplast and are maintained for 24 hours. Rate of absorption is controlled by the skin.

5.3 Preclinical safety data

Glyceryl trinitrate showed mutagenic activity against one strain of *Salmonella typhimurium* and carcinogenicity in an oral long term study in rats, with increased incidence of hepatocellular carcinomas and interstitial tumours of the testis. However, carcinogenicity in rats occurred at high doses, and glyceryl trinitrate was not carcinogenic in mice. Moreover, it was not mutagenic against other bacterial strains and in other tests, including *in vivo* tests. The risk of carcinogenicity following the therapeutic use of the medicinal product is considered negligible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acrylic adhesive containing 2- ethylhexylacrylate, vinyl acetate, acrylic acid and aluminium (tris)acetylacetoneate
Polyolefin film
White printing ink
Silicone-coated polyester film

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Patches are individually packaged in sachets constructed from Paper/LDPE/Aluminium foil/LDPE film and contained in a cardboard carton.

Pack sizes: 7, 10, 15, 28, 30 and 100 transdermal patches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Cardioplast transdermal patch should be used according to the instruction under section 4.2.

Patients should be advised to dispose of patches carefully to avoid accidental application or use.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited
T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA577/174/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 19th July 2013

10 DATE OF REVISION OF THE TEXT