IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1260/004/001
Case No: 2071684

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Cephalon Limited

1 Albany Place, **Hyde Way**, **Welwyn Garden City**, **Hertfordshire AL7 3BT**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Dopacard 10mg/ml Concentrate for Solution for Infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **13/04/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dopacard 10mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml ampoule contains 50mg dopexamine hydrochloride (10mg/ml).

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Dopacard is indicated for short term administration (experience in clinical studies has included administration for up to 48h) to patients who require peripheral vasodilator (afterload reduction), renal vasodilator and mild positive inotropic therapy in the treatment of heart failure such as may be associated with exacerbation of chronic heart failure or with cardiac surgery. Dopexamine should only be used in specialist units in which adequate facilities are available for patient surveillance and monitoring of responses.

4.2 Posology and method of administration

Dosage
The dosage required is variable and must be determined for each patient by dose titration. Patients who are acutely ill wi a high sympathetic drive may require and tolerate lower doses than those with severe chronic disease.

Adults and the elderly:
Infusion should begin at a dose of 0.5 microgram/kg/min and may be increased to 1 microgram/kg/min and then in increments (0.5-1 microgram/kg/min) up to 6 micrograms/kg/min at not less than 15 minute intervals according to the patient's haemodynamic and clinical response. Smaller increments (0.5 microgram/kg/min) may be justified in certain patients according to haemodynamic and clinical response.

Children:
The safety and efficacy of Dopacard for use in children have not been established.

Administration:
Dopacard should be only administered intravenously by infusion through a cannula or catheter in a central or large peripheral vein.

Contact with metal parts in infusion apparatus should be minimised. A device which provides accurate control of the rate of flow is essential.

Central administration:
Dopacard can be administered via a cannula or catheter sited in a central vein. The concentration of the infusion solution for administration via this route must not exceed 4mg/ml.

Peripheral Administration:
Dopacard can be administered via a cannula in a large peripheral vein. The concentration of the infusion solution for administration via this route must not exceed 1mg/ml. Thrombophlebitis has occasionally been reported with peripheral administration using concentrations of Dopacard exceeding 1 mg/ml.

During the administration of Dopacard, as with any parenteral catecholamine, the rate of administration and duration of therapy should be adjusted according to the patient's response as determined by heart rate and rhythm (ECG), blood pressure, urine flow and, if possible, measurement of cardiac output.

It is recommended that the infusion of Dopacard is reduced gradually rather than withdrawn abruptly.

The duration of therapy is dependent upon the patient's overall response to treatment. Extended therapy beyond 48 hours has not been fully evaluated.

Special instructions for the preparation of Dopacard Infusion Solutions:
Dopacard must be diluted before use. For instructions on dilution of the product before administration see section 6.6

4.3 Contraindications

Known sensitivity to dopexamine hydrochloride or excipients (disodium edetate).

Use in patients who are receiving monoamine oxidase inhibitors (MAOIs) or have received such treatment within the past 14 days.

Phaeochromocytoma.

Thrombocytopenia.

Use in patients with left ventricular outlet obstruction such as hypertrophic obstructive cardiomyopathy or aortic stenosis. In such patients, positive inotropic activity may increase left ventricular outflow obstruction and sudden vasodilatation may cause hypotension.

Use in patients with uncorrected hypovolaemia.

4.4 Special warnings and precautions for use

Correction of hypovolaemia must be achieved before the administration of Dopacard. Hypovolaemia should also be corrected during therapy as vasodilatation occurs due to treatment.

Care should be exercised so as to restrict the sodium and fluid load during administration of Dopacard.

Dopacard should not be administered to patients with severe hypotension or a markedly reduced systemic vascular resistance until specific resuscitative measures have been taken to restore blood pressure to a clinically acceptable level.

In patients with a marked reduction in systemic vascular resistance, Dopacard should not be used as a direct substitute for pressor agents or other inotropes.

As with other catecholamines, Dopacard should be administered with caution to patients with a clinical history of ischaemic heart disease especially following acute myocardial infarction or recent episodes of angina pectoris as a tachycardia may increase myocardial oxygen demand and further exacerbate myocardial ischaemia.

As has been observed with some other b_2-adrenergic agonists, a small reversible fall in circulating platelet numbers has been observed in some patients. No adverse effects attributable to alterations in platelet count have been seen in clinical trials.

Care must be exercised when administering Dopacard in the presence of hypokalaemia or hyperglycaemia. In common with other b_2-agonists, Dopacard depresses plasma potassium and raises plasma glucose. These effects are minor and reversible. Monitoring of potassium and glucose is advisable in patients likely to be at risk from such changes, e.g. diabetics, patients with myocardial infarction or patients being treated with diuretics or cardiac glycosides.

Benign arrhythmias such as ventricular premature beats and, more rarely, serious arrhythmias have been reported in some patients. If excessive tachycardia occurs during Dopacard administration, then a reduction or temporary discontinuation of the infusion should be considered.

As with other parenteral catecholamines, there have been occasional reports of partial tolerance, with some attenuation of the haemodynamic response developing during long-term infusions of Dopacard.

The risk of thrombophlebits and local necrosis may be increased if the concentration of Dopacard administered via a peripheral vein exceeds 1 mg/ml. Thrombophlebits is rare when the concentration of drug used for peripheral administration is less than 1mg/ml.

4.5 Interaction with other medicinal products and other forms of interaction

As Dopacard inhibits Uptake-1, it may potentiate the effects of exogenous catecholamines such as noradrenaline. Caution is recommended when these agents are administered concomitantly with Dopacard or soon after discontinuation of its use.

In the case of dopamine, there is no evidence of an interaction, other than possible attenuation of the indirect sympathomimetic inotropic effects of higher doses of dopamine due to Uptake-1 blockade by Dopacard.

Concomitant use with b_2-adrenergic antagonists and dopamine receptor antagonists requires caution since attenuation of the pharmacological effects of Dopacard may occur.

4.6 Pregnancy and lactation

There is no experience of the use of Dopacard in pregnant or lactating women and therefore its safety in these situations has not been established. There is insufficient evidence from animal studies to indicate it is free from hazard. Dopacard is not therefore currently recommended for use in pregnant or lactating women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The most common undesirable effect reported with Dopacard administration is tachycardia (11.8% in studies of acute exacerbations of chronic heart failure; 19.4% in studies of use in cardiac surgery). The increases in heart rate are dose related and in most cases not clinically significant.

Other undesirable effects reported in clinical trials in both acute exacerbations of chronic heart failure and cardiac surgery at an incidence of 1% or more include:

Cardiovascular: A number of tachyarrhythmias such as premature ventricular contractions (PVCs) and atrial fibrillation; bradycardia, both sinus and nodal; worsening heart failure leading to asystole and cardiac arrest; angina; myocardial infarction; cardiac enzyme changes and non-specific ECG changes. Hypotension and hypertension have also been reported, the latter with a higher incidence in patients following cardiac surgery.

Non-cardiovascular: Nausea and vomiting; tremor; headache; diaphoresis and dyspnoea.

Careful titration of the dose may minimise the incidence of adverse events.

More rarely a number of serious adverse events have been reported in patients undergoing cardiac surgery: renal failure, acute respiratory distress syndrome (ARDS), pulmonary oedema, pulmonary hypertension, bleeding and septicaemia. However, such events may also be due to the condition of the patients in such a population.

4.9 Overdose

The half-life of Dopacard in blood is short (approximately 6 - 7 minutes in healthy volunteers and around 11 minutes in patients with cardiac failure).
Consequently, the effects of overdosage are likely to be short-lived provided that administration is discontinued. Effects of overdosage are likely to be related to the pharmacological actions and include tachycardia, tremulousness and tremor, nausea and vomiting, and anginal pain. Treatment should be supportive and directed to these symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The primary actions of Dopacard (dopexamine hydrochloride) are the stimulation of adrenergic b_2-receptors and peripheral dopamine receptors of DA_1 and DA_2 subtypes. In addition, Dopacard is an inhibitor of neuronal re-uptake of noradrenaline (Uptake-1). These pharmacological actions result in an increase in cardiac output mediated by afterload reduction (b_2, DA_1) and mild positive inotropism (b_2, Uptake-1 inhibition) together with an increase in blood flow to vascular beds (DA_1) such as the renal and mesenteric beds and also peripherally. Dopacard is not an a-adrenergic agonist and does not cause vasoconstriction and is not a pressor agent.

Experience in clinical trials has shown that Dopacard can increase cardiac output by over 100% within the recommended dose range and increases of the order of 50% are frequently achieved at doses of 1-2 micrograms/kg/min without a clinically significant effect on heart rate.

5.2 Pharmacokinetic properties

Dopacard is readily eliminated from blood with a half-life of approximately 6-7 minutes in healthy volunteers and around 11 minutes in patients with cardiac failure. Subsequent elimination of the metabolites is by urinary and biliary excretion. The response to Dopacard is rapid in onset and effects subside rapidly on discontinuation of the infusion. Increases in dose may be made at intervals of not less than 15 minutes.

5.3 Preclinical safety data

There are no additional safety data of relevance to the prescriber which have not already been stated in the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Hydrochloric acid
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6
Dopacard should not be added to Sodium Bicarbonate or any other strongly alkaline solution, as inactivation will occur.

Contact with metal parts, in infusion apparatus for example, should be minimised.

6.3 Shelf Life

The shelf life for unopened ampoules is three years.

Chemical and physical in-use stability of prepared intravenous solutions in 0.9% Sodium Chloride Injection or 5% Dextrose Injection has been demonstrated for 24 hours at 25ºC.

From a microbiological point of view, the product should be diluted and used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25ºC. Keep the ampoule in the outer carton in order to protect from light and moisture.
For storage of sterile products that have been opened, diluted, or reconstituted see section 6.3.

6.5 Nature and contents of container

Box of 10 clear Type I glass ampoules each containing 5ml of 1% (w/v) solution of dopexamine hydrochloride (50mg per ampoule).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Dopacard should only be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Hartmann's Solution (Compound Sodium Lactate Intravenous Infusion) or Dextrose 4%/Saline 0.18% Injection.

The appropriate volume of diluent solution should be aseptically extracted from the infusion bag, or the metering chamber of the administration set, before adding the contents of the Dopacard ampoule(s) to arrive at the final concentration - see table below.

Care should be exercised in heart failure to restrict the sodium load and volume being administered.

Volume of diluent solution (ml)	Volume to be extracted (ml)	No. of 5 ml Dopacard ampoules to be added	Final Concentration (µg/ml)
100	5	1	500
250	10	2	400
500	20	4	400
250	20	4	800

Dopacard, in common with other catecholamines, may turn slightly pink in prepared solutions. There is no significant loss of potency associated with this change.

7 MARKETING AUTHORISATION HOLDER

Cephalon Limited
1 Albany Place
Hyde Way
Welwyn Garden City
Hertfordshire
AL7 3BT
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1260/4/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 October 1988

Date of last renewal: 14 June 2009

10 DATE OF REVISION OF THE TEXT

March 2010