SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perfan® Injection 100 mg/20 ml concentrate for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Enoximone solution 5 mg/ml presented in ampoules containing 20 ml.

Excipients with known effect
Each ampoule of 20 ml contains
–8.76 g propylene glycol
–10.4 vol % ethanol

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Perfan Injection is indicated for the short-term treatment of congestive heart failure, typically where cardiac output is reduced and filling pressures increased, in patients who require intravenous therapy and who can be closely monitored.

4.2 Posology and method of administration

Perfan Injection is for intravenous administration (slow injection or continuous infusion) and must be diluted before use.

Dilution
The pH of Perfan Injection is approximately 12.0. Perfan Injection must be diluted with an equal volume of 0.9 % sodium chloride injection or water for injections before administration.

Do not use more dilute solutions or other diluents, particularly dextrose injection, as crystal formation may occur.

Use only plastic containers or syringes for dilution. When Perfan Injection has been diluted in glass containers or syringes, crystal formation has been observed within approximately 1 hour.

Method of Administration
The following procedure is recommended for the administration of the diluted Perfan® Injection.

Initial Therapy
Therapy should be initiated with a dose of 0.5 - 1.0 mg/kg given as a slow intravenous injection (not faster than 12.5 mg/min); further doses of 0.5 mg/kg may be given similarly every 30 minutes until a satisfactory response is achieved or a total initial dose of 3.0 mg/kg is reached. Alternatively, treatment may be initiated as an infusion at a rate of 90 µg/kg/minute administered over 10 - 30 minutes until the required haemodynamic response is achieved.

Maintenance Therapy
To maintain the effects of Perfan Injection the initial dose (not more than 3.0 mg/kg) may be repeated as required every 3 - 6 hours and adjusted according to the response of the patient: Alternatively, a continuous or intermittent infusion at a rate of 5 to 20 µg/kg/minute may be instituted. The total dose over 24 hours should not normally exceed 24.0 mg/kg. In patients with renal impairment the dosage or dosage frequency may need to be reduced.

This dosing regimen will produce, in the majority of patients, a 30 % or greater increase in cardiac output and/or decreases in pulmonary capillary wedge pressure of about 30 % and right atrial pressure of about 40 %. It should be noted that the initial haemodynamic response determines the subsequent rate of administration as well as the duration of treatment.

Precautions should be taken to avoid venous extravasation during administration.

The duration of therapy should depend on the patient's continued positive and beneficial response. Sustained haemodynamic and clinical effects have been observed in patients treated for up to 48 hours.

Use in children
Safety and effectiveness in children have not been established. There is no experience in children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Perfan Injection should be used cautiously when heart failure is associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction. Blood pressure and heart rate should be closely monitored during intravenous administration of Perfan Injection. In patients who show symptomatic decreases in blood pressure, Perfan Injection should be administered at a reduced rate or, if necessary, should be stopped.

Patients with severe congestive heart failure have a high incidence of arrhythmias and are particularly vulnerable to the development of arrhythmias. It is recommended that patients be observed closely while receiving Perfan Injection.

Electrolyte and Fluid Balance

Fluid and electrolyte status and renal function should be assessed during therapy with Perfan Injection. Improvement in cardiac output with associated diuresis may require a reduction in the dose of diuretic drugs. Abnormal serum potassium levels (which may be due to excessive diuresis) may predispose patients to arrhythmias especially those on digitalis. Therefore, serum potassium levels should be monitored carefully and corrective measures should be instituted before or during therapy with Perfan Injection. Hypovolaemia with inadequate cardiac filling pressure (which may be due to diuretic therapy) may prevent patients from responding adequately to Perfan Injection. Fluid and electrolyte status should be continuously monitored and corrective measures should be instituted before or during therapy with Perfan Injection.

Management of Adverse Reactions

Arrhythmias

The occurrence of severe supraventricular and ventricular arrhythmias may require immediate discontinuation of Perfan Injection and institution of appropriate antiarrhythmic therapy.

Platelet Count Reduction

Platelet counts before and during therapy are recommended.

Gastrointestinal Side Effects

Severe gastrointestinal side effects may be managed by reducing dosage, or if necessary, administration of Perfan Injection may be temporarily interrupted.

Increases in Hepatic Enzyme Levels

It is recommended to monitor patients for changes in hepatic enzyme levels. If clinically significant increases in hepatic enzymes occur following the

intravenous administration of Perfan Injection, therapy should be discontinued.

This medicinal product contains 10.4 vol % ethanol (alcohol), i. e. up to 37.44 g in the maximum daily dose of 360 mL (based on the recommendation that the total daily dose should not exceed 24 mg/kg and assuming a patient with 75 kg), equivalent to appr. 750 ml beer resp. 300 ml wine per maximum daily dose.
Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease or epilepsy.
The amount of alcohol in this medicinal product may alter the effects of other medicines.
The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

This medicine contains less than 1 mmol sodium (23 mg) per 20 ml-ampoule, that is to say essentially ‘sodium-free’.

This medicinal product contains propylene glycol. Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol.
Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis.
Medical monitoring is required.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

No clinical manifestations of untoward drug interaction were observed in patients receiving Perfan Injection most of whom concomitantly received one or more of the following: diuretics (amiloride, triamterene, frusemide and spironolactone), digitalis glycosides (digoxin), potassium supplements, antiarrhythmics (diltiazem, propranolol, lignocaine, nifedipine, procainamide and quinidine), vasodilators (captopril, hydralazine, nitroprusside and nitrates), anticoagulants (warfarin and heparin), analgesics (acetylsalicylic acid, paracetamol and codeine), sedatives (chloral hydrate, diazepam and lorazepam) and positive inotropic agents (dobutamine and dopamine).

In general, administration of Perfan Injection has not been associated with clinically significant alterations in laboratory tests. However, some changes have been noted in platelet counts (reduction in a small percentage of patients) and hepatic enzyme levels (a few patients with minor abnormalities). Monitoring of these parameters is recommended.

4.6 Fertility, Pregnancy and lactation

There is no evidence of animal teratogenicity with oral therapy. Reproduction studies performed in rats at doses up to 300 mg/kg/day and 100 mg/kg/day have revealed reductions in maternal food consumption, maternal body weight gain and in pup weight at weaning and sexual maturity when enoximone was administered throughout pregnancy and lactation. Sexual behaviour and reproductive capability were unaltered by enoximone treatment.

There are no adequate data from the use of enoximone in pregnant women. Perfan Injection should not be used during pregnancy unless clearly necessary.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Perfan Injection is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Not relevant. Perfan Injection is used in hospitalised patients.

4.8 Undesirable effects

The following undesirable effects have been reported:

Common (>1/100 to <1/10):

- hypotension*
- insomnia
- headache
- platelet count reduction (without clinical symptoms, e. g. petechiae, purpura or bleeding)*
- rise in transaminases and bilirubin*

Uncommon (>1/1.000 to <1/100):

- ventricular tachycardia and supraventricular arrhythmia (e. g. ectopia, tachycardia, tachyarrhythmia)
- dizziness
- vomiting
- nausea
- diarrhoea
- slight rise in blood glucose and alkaline phosphatase
- slight rise in leukocytes (particularly neutrophils, eosinophils)
- slight decrease in haematocrit and haemoglobin
- slight rise in urea, creatinine or uric acid

Rare (>1/10.000 to <1/1.000):
- (thrombo-) phlebitis at the site of injection
- fever
- chills
- urinary retention
- oliguria
- fluid retention
- irritation
- muscle pain in extremities

Very rare (<1/10.000):
- ventricular fibrillation, particularly at doses of > 3 mg/kg BW*

* see section 4.4 'Special warnings and precautions for use'

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 the national report system:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Intravenous administration of Perfan Injection has been shown to produce reductions in blood pressure with occasional instances of hypotensive symptoms. If symptomatic hypotension is observed, administration of Perfan Injection should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

Perfan Injection has been shown to have a low degree of acute toxicity in rats and mice. The oral LD_{50} of enoximone suspension exceeded 5000 mg/kg in both male and female rats and mice, while the intraperitoneal LD_{50} exceeded 2500 mg/kg in male and female rats and male mice; in female mice it was between 1600 and 2500 mg/kg. The true acute intravenous LD_{50} could not be determined because of the toxicity of the vehicle (approximately 12 ml/kg).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Phosphodiesterase inhibitors, ATC code: C01CE03.

Enoximone is an inodilator possessing both positive inotropic and vasodilator properties. It differs in structure and mode of action from digitalis glycosides and catecholamines.

The exact mechanism of the inotropic and vasodilator effects of enoximone is not completely understood; however, animal studies have shown that the positive inotropic activity is direct and apparently results, at least in part, from a selective inhibition of cardiac phosphodiesterase III with a subsequent increase in cellular levels of cAMP. Enoximone has no significant direct effect on adenylate cyclase activity. Na^+, K^+ – ATPase activity, Ca^{++} – uptake by sarcoplasmic reticulum. The vasodilation activity is also direct and does not involve either blockade or stimulation of adrenergic receptors.

5.2 Pharmacokinetic properties

The median half-life of enoximone was 4.2 hours in normal subjects and 6.2 hours in congestive heart failure patients. In the latter group who received single i.v. doses of 0.5 to 3.0 mg/kg, apparent total body clearance ranged from 3.7 to 13.0 ml/min/kg, and volume of distribution at steady state ranged from 1.1 to 3.6 l/kg. With continuous infusion at higher doses, the median clearance and median elimination half-life were 6.3 ml/min/kg and about eight hours, respectively. In patients with congestive heart failure a loading dose of 90 µg/kg/min over 20 - 60 minutes followed by an average maintenance infusion of 1.0 mg/min (range 0.5 - 1.25) over 48 hours maintained mean plasma levels at about 3.6 µg/ml and 9.7 µg/ml for the parent compound and active sulphoxide metabolite, respectively. The primary route of elimination in man is via the kidney (or urine) following biotransformation to the sulphoxide, the principal urinary excretion product. On average, 78 % of an oral dose is recoverable as the cardioactive sulphoxide metabolite in an 8-hour urine collection.

Enoximone is approximately 85 % plasma protein bound and it is unlikely, therefore, that clinically significant drug interactions will occur as a result of displacement from protein binding.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, sodium hydroxide, propylene glycol and water for injections.

6.2 Incompatibilities

Perfan Injection must only be diluted with 0.9 % sodium chloride injection or water for injections.

Do not use other diluents, particularly dextrose injection, as crystal formation has been observed after mixing.

Perfan Injection must not be mixed in glass containers or syringes as crystal formation has been observed within approximately 1 hour after mixing. Only plastic containers or syringes should be used for dilutions.

Other drugs or fluids must not be mixed in the same container or administered concomitantly in the same infusion line as Perfan Injection.

6.3 Shelf life

3 years unopened.

Chemical and physical in-use stability has been demonstrated for 24 hours at 5 °C and 25 °C. From a microbiological point of view, the product should be used immediately. 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 room temperature unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25 °C.

After dilution, the product must be stored at room temperature. Dilutions must not be refrigerated as crystal formation may occur.

6.5 Nature and contents of container

Glass ampoules (Type I Ph. Eur.) of 20 ml (100 mg enoximone/ampoule) in cartons containing 5 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

MACURE PHARMA UK LTD
3 Waterhouse Square,
138-142 Holborn, London
EC1N 2SW

8 MARKETING AUTHORISATION NUMBER(S)

PL 54594/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 January 2010

10 DATE OF REVISION OF THE TEXT

05/02/2024