Prescribing Information

For the use of Registered Medical Practitioner, Hospital or a Laboratory Only.

EURYTHMIC
50 mg/ml Injection

Sterile Amiodarone Concentrate BP 50 mg/ml

COMPOSITION :
Each ml contains :
Amiodarone Hydrochloride BP 50 mg.

DESCRIPTION :
Clear pale yellow liquid.
Eurythmic contains amiodarone HCl, a class III antiarrhythmic drug.

CLINICAL PHARMACOLOGY :
Amiodarone is a class III antiarrhythmic drug, but possesses electrophysiologic characteristics of all four Vaughan Williams classes. Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, it exerts a noncompetitive antisympathetic action. One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a class III effect. The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of class IV drugs. In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisympathetic action and the block of calcium and potassium channels are responsible for the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node. Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption.
I.V. amiodarone prolongs intranodal conduction and refractoriness of the AV node, but has little effect on sinus cycle length, refractoriness of the right atrium and right ventricle, repolarization (QTc), intraventricular conduction (QRS), and infranodal conduction.
The initial acute effects of amiodarone I.V. may be focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (class IV activity) and noncompetitive adrenergic antagonism (class II activity).
Pharmacokinetics and Metabolism : Amiodarone exhibits complex disposition characteristics after IV administration. Peak serum concentrations after single 5 mg/kg 15-minute intravenous infusions in healthy subjects range between 5 and 41 mg/L. Peak concentrations after 10-minute infusions of 150 mg amiodarone in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) range between 7 and 26 mg/L. Due to rapid distribution, serum concentrations decline to 10% of peak values within 30 to 45 minutes after the end of the infusion.
N-desethylamiodarone (DEA) is the major active metabolite of amiodarone. DEA serum concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion. Amiodarone is metabolized to DEA by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P450 3A4 (CYP3A4) and CYP2C8. The CYP3A4 isoenzyme is present in both the liver and intestines. Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion in urine. Neither amiodarone nor DEA is dialyzable. Amiodarone and DEA cross the placenta and both appear in breast milk. DEAs precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain.
Age, sex, renal disease, and hepatic disease (cirrhosis) do not have marked effects on the disposition of amiodarone or DEA. After a single dose of I.V. amiodarone in cirrhotic patients, significantly lower Cmax and average concentration values are seen for DEA, but mean amiodarone levels are unchanged. Normal subjects over 65 years of age show lower clearances (about 100 mL/hr/kg) than younger subjects (about 150 mL/hr/kg) and an increase in half life(t1/2) from about 20 to 47 days. In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal disposition t1/2 of DEA is prolonged. Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.
There is no established relationship between drug concentration and therapeutic response for short-term intravenous use.

INDICATIONS :
Treatment of severe rhythm disturbances especially the following : Atrial arrhythmia with rapid ventricular rhythm, tachycardia associated with Wolff-Parkinson-White syndrome and ventricular rhythm disorders. Cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock.
Amiodarone I.V. is to be used where a rapid response is required or where oral administration is not possible.

DOSAGE AND ADMINISTRATION :

Treatment of severe rhythm disturbances when oral use is not suitable, except for cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock
I.V. Infusion : Loading Dose: Usual dosage is 5 mg/kg body weight administered in glucose solution exclusively over a period of 20 min-2 hrs; infusion may be repeated 2-3 times/24 hrs. The rate of infusion should be adjusted on the basis of results. Therapeutic effect appears within the 1st minutes and then progressively decreases. Therefore, an infusion should be set up to take over.
Maintenance Dosage : 10-20 mg/kg body weight/24 hrs (usually 600-800 mg/24 hrs and up to 1200 mg/24 hrs) in 250 mL dextrose over a few days. Replaced by oral administration (600 mg/day) from the 1st day of infusion. May be increased to 800 mg or 1000 mg /day.
Cardiopulmonary resuscitation in the event of cardiac arrest related to ventricular fibrillation resistant to external electric shock :
As regards the administration route and in view of the situation in which this indication applies, the use of a central venous catheter is recommended if immediately available; otherwise, the medicinal product may be administered via the peripheral venous route using the largest peripheral vein with the highest flow possible.

- The initial intravenous dose is 300 mg (or 5 mg/kg) diluted in 20 ml of 5% glucose solution and rapidly injected.
- Additional intravenous administration of 150 mg (or 2.5 mg/kg) may be considered if ventricular fibrillation persists.
- Do not add any other products to the syringe.

CONTRAINDICATIONS :
Amiodarone I.V. is contraindicated in patients with known hypersensitivity to any of the components of amiodarone I.V., including iodine, or in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block unless a functioning pacemaker is available.

WARNINGS :

This product is to be used only by a registered medical practitioner with experience in cardiology.

I.V. injection is generally not advised because of the possible hemodynamic risks (severe hypotension, circulatory collapse); I.V. infusion is preferred whenever it is possible.
I.V. injection is to be done only in emergency circumstances where alternative therapies have failed and only in a cardiac intensive care unit under continuous electrocardiographic monitoring (ECG, blood pressure).
I.V. injection is contraindicated in case of hypotension, severe respiratory failure, cardiomyopathy or heart failure (possible worsening).
Dosage is around 5 mg/kg body weight to be injected over a minimum of 3 min.
I.V. injection should not be repeated <15 min following the 1st injection even if the latter was of 1 amp only (possible irreversible collapse).
Do not mix with other preparations in the same syringe. Do not inject other preparations in the same line. Continued treatment should be via I.V. Infusion.
Use in children : As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

PRECAUTIONS :
Electrolyte balance disturbances and, in particular; hypokalaemia: it is important to take into account situations that may be associated with hypokalaemia since the latter can promote the onset of proarrhythmic effects. Hypokalaemia should be corrected prior to administration of amiodarone.
The undesirable effects are usually related to excessive medicine levels; they can be avoided or their severity minimized by carefully seeking the minimum maintenance dosage. Patients should be advised to avoid exposure to sun or to use sun protection during treatment.
Amiodarone can cause thyroid anomalies. Assay of TSH is recommended in all patients before treatment and then regularly throughout treatment - for example, every 6 months - and several months after its withdrawal. TSH levels should be measured in the event of clinical suspicion of dysthyroidism.
In children, the safety and efficacy of amiodarone have not been evaluated by controlled clinical trials.
Regular monitoring of liver function (transaminases levels) is useful to screen for liver damage caused by amiodarone.
Anaesthesia : Before surgery, the anaesthetist must be informed that the patient is treated with amiodarone.
Chronic treatment with amiodarone may lead to exacerbation, in terms of undesirable effects, of the haemodynamic risks of general or local anaesthetics. These concern, in particular, bradycardiac and hypotensive effects, reduce cardiac output and conduction disturbances.
In addition, a few cases of acute respiratory distress have been observed immediately after surgery in patients treated with amiodarone. Consequently, close monitoring is recommended during artificial ventilation of such patients.
Effects on the Ability to Drive or Operate Machinery : Not relevant.
Incompatibility : Amiodarone hydrochloride is incompatible with saline solution and may only be administered in a 5% w/v Glucose intravenous infusion.
In the presence of amiodarone the use of administration equipment containing softening agents such as DEHP (di-2-ethylhexyl phthalate) may cause DEHP to

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leach in to the solution. In order to minimise patient exposure to DEHP, diluted amiodarone solutions for infusion should be administered through sets that do not contain DEHP, such as polyolefin (PE, PP) or glass sets. No other agents may be added to amiodarone infusions.

This medicinal product must not be mixed with other medicinal products except those mentioned in dosage and administration.

Pregnancy & Lactation : I.V. amiodarone should be used during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

Amiodarone and DEA, are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. The risk of exposing the infant to amiodarone should be weighed against the potential benefit of arrhythmia suppression in the mother. The mother should be advised to discontinue nursing.

It is not known whether the use of amiodarone during labor or delivery has any immediate or delayed adverse effects.

Pediatric use : The safety and efficacy of amiodarone in the pediatric population have not been established; therefore, its use in pediatric patients is not recommended.

Amiodarone I.V. contains benzyl alcohol. There have been reports of fatal "gasping syndrome" in neonates following the administration of intravenous solutions containing benzyl alcohol. Symptoms include a striking onset of gasping respiration, hypotension, bradycardia, and cardiovascular collapse.

Geriatric use : In general, dose selection for an elderly patient should be cautious, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Transplantation

In retrospective studies, amiodarone use in the transplant recipient prior to heart transplant has been associated with an increased risk of primary graft dysfunction (PGD).

PGD is a life-threatening complication of heart transplantation that presents as left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section Adverse Effects). Severe PGD may be irreversible.

For patients who are on the heart transplant waiting list, consideration should be given to use an alternative antiarrhythmic drug as early as possible before transplant.

DRUG INTERACTIONS :

Interactions with other medicinal products and other forms of interaction : A number of antiarrhythmics drugs depress cardiac automatism, conduction and contractility. The combination of antiarrhythmics from different classes can provide a beneficial therapeutic effect, but is usually very delicate, requiring close clinical and ECG monitoring. The combination of antiarrhythmics inducing torsades de pointes (eg, amiodarone) is contraindicated. The combination of antiarrhythmic from the same class is not recommended, apart from in exceptional cases, due to the increased risk of cardiac undesirable effects. Combination with medicines with negative inotropic, bradycardiac and/or atrioventricular conduction slowing drugs is delicate and requires close clinical and ECG monitoring.

Contraindicated Combinations : Medicinal products that can induce torsades de pointes: Class-Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide); Class III antiarrhythmics (dofetilide, ibutilide, sotalol); Other medicinal products, such as: Bepridil, cisapride, diphemanil, erythromycin I.V., mizolastine, vincamine I.V.; Sultopride increase risk of ventricular arrhythmia and, in particular, torsades de pointes.

Sparfloxacin : Risk of torsades de pointes due to a prolongation in QT interval (addition of electrophysiological effects).

Inadvisable Combinations : Neuroleptics inducing torsades de pointes: Some phenothiazine neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzaminde neuroleptics (amisulpride, sulpiride, tiapride), butyrophenone neuroleptics (droperidol, haloperidol), other neuroleptics (pimozide) increased risk of ventricular arrhythmia and, in particular, torsades de pointes.

Halofantrine, Moxifloxacin, Pentamidine : Increased risk of ventricular arrhythmia and, in particular, torsades de pointes. If possible, suspend the non-antibiotic torsadogenic medicine. If the combination cannot be avoided, prior control of QT interval and constant electrocardiographic monitoring.

Injectable Diltiazem : Risk of bradycardia and atrioventricular block. If this combination cannot be avoided, only administer under close clinical and constant electrocardiographic monitoring. Beta-blockers (other than sotalol and esmolol) contractility, automatism and conduction disturbances (suppression of compensatory sympathic mechanisms).

Combinations requiring precaution for use : Oral Anticoagulants: Increased anticoagulant effect and haemorrhagic risk. More frequent control of prothrombin rate and monitoring of INR. Adjustment of oral anticoagulant dosage during treatment with amiodarone and after its withdrawal.

Ciclosporin : Increase in circulating levels of the immunosuppressant medicine due to a reduction in its hepatic metabolism with a risk of nephrotoxic effects. Assay of blood concentrations of the immunosuppressant medicine, monitoring of kidney function and adjustment of dosage during the combination and after its withdrawal.

Oral Diltiazem : Risk of bradycardia or atrioventricular block, particularly in the elderly. Clinical and electrocardiographic monitoring.

Digitalis Drug : Depression of automatism (excessive bradycardia) and atrioventricular conduction disturbances. In the event of use of digoxin, increased blood digoxin levels due to reduced digoxin clearance. Clinical and electrocardiographic monitoring and, if necessary, monitoring of blood digoxin levels and adjustment of digoxin dosage.

Esmolol : Contractility, automatism and conduction disturbances (suppression of compensatory sympathetic mechanisms). Clinical and electrocardiographic monitoring.

Potassium-lowering Drugs : Potassium-lowering diuretics (alone or in combination), stimulant laxatives, glucocorticoids (systemic route), tetracosactide, amphotericin B (IV route) increased risk of ventricular arrhythmia and, in particular, torsades de pointes. Clinical, electrolyte and electrocardiographic monitoring.

Phenytoin : Increase in plasma concentrations of phenytoin with signs of overdose and, in particular, neurological signs (reduced hepatic metabolism of phenytoin). Clinical monitoring, control of plasma concentrations of phenytoin and, if necessary, adjustment of the latter's dosage.

Bradycardiac Drugs : Bradycardiac calcium antagonists (diltiazem, verapamil), beta-blockers (except sotalol), clonidine, guanfacine, digitalis drugs, mefloquine, anticholinesterase drugs (donepezil, galantamine, rivastigmine, tacrine, ambenonium, pyridostigmine, neostigmine) Increased risk of ventricular arrhythmia and, in particular, torsades de pointes. Clinical and electrocardiographic monitoring.

Simvastatin : Increased risk of undesirable effects (dose-dependent), such as rhabdomyolysis (reduced hepatic metabolism of the cholesterol-lowering drug). Do not exceed a dosage of 20mg/d simvastatin.

If the therapeutic goal is not achieved at this dosage, use another statin not concerned by this type of interaction.

General Anaesthesia : Potentially severe complications have been reported in patients undergoing general anaesthesia: Bradycardia (unresponsive to atropine), hypotension, conduction disorders, decreased cardiac output. Very rare cases of severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal, have been observed usually in the period immediately following surgery. A possible interaction with a high oxygen concentration may be implicated.

Caution for usage : Because of pharmaceutical characteristics, concentrations <600 mg/L should not be used. Only 5% dextrose should be used. Do not mix with other preparations in infusion solution.

ADVERSE EFFECTS :

The most important treatment-emergent adverse effects were hypotension, asystole/cardiac arrest/electromechanical dissociation (EMD), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. The most common adverse effects leading to discontinuation of amiodarone I.V. therapy were hypotension, asystole/cardiac arrest/EMD, VT and cardiogenic shock. Fever and nausea were also reported.

Infrequently reported adverse events include abnormal kidney function, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, prolonged QT interval, respiratory disorder, shock, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

Injury, poisoning and procedural complications:

Frequency 'not known': Potentially fatal primary graft dysfunction post cardiac transplant (See section Warnings and Precautions).

OVERDOSAGE :

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of amiodarone I.V. include hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity. Hypotension and cardiogenic shock should be treated by slowing the infusion rate or with standard therapy : vasopressor drugs, positive inotropic agents, and volume expansion. Bradycardia and AV block may require temporary pacing. Hepatic enzyme concentrations should be monitored closely. Amiodarone is not dialyzable.

STORAGE :

Unopened Ampoule: Store below 30°C, protected from light.

After dilution: Eurythmic Injection has been found to be stable at 30°C temperature for 24 hours after dilution in the 5% Dextrose in Water when diluted solution placed in Glass Container (USP Type I), Polyolefin Container, and 2 hours after dilution in the 5% Dextrose in Water when diluted solution are placed in PVC Container.

PRESENTATION :

Available in 3 ml amber ampoule. Such 5 ampoules are packed in a carton.

DATE OF REVISION :

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Manufactured by :

Troikaa

Troikaa Pharmaceuticals Ltd.

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