PACKAGE INSERT

Scheduling status: S4

Proprietary name and dosage form:

AMIODARONE 150MG/3ML OETHMAAN (intravenous injection)

Composition:

Each 3ml of solution contains amiodarone hydrochloride 150mg

Pharmacological classification:

A 6.2 Cardiac depressants

Pharmacological action:

Amiodarone prolongs the duration of the action potential, particularly in the nodal and Purkinje tissue. Amiodarone does not appear to alter the resting membrane potential, but depresses membrane responsiveness, and prolongs the refractory period in the atria, AV node, His-Purkinje system, ventricles and accessory atrioventricular conduction pathways. Amiodarone also demonstrates non-competitive alpha- and beta-adrenoreceptor antagonism.

Indications:

Where rapid response is requires in the control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome and other types of tachyarrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardias, atrial flutter and atrial fibrillations and ventricular fibrillations which have proved to be resistant to other anti-arrhythmic therapy.

Contra-indications:

AMIODARONE 150MG/3ML OETHMAAN should not be used when the following medical problems exist:

- Hypersensitivity to amiodarone
- Atrioventricular (AV) block, pre-existing 2nd or 3rd degree, without pacemaker (risk of complete heart block).
- Bradycardic episodes resulting in syncope, unless controlled by pacemaker.
- Severe sinus node function impairment, causing marked sinus bradycardia, unless controlled by pacemaker (AMIODARONE 150MG/3ML OETHMAAN reduces sinus node automaticity and may cause atropine-resistant sinus bradycardia).
- Acute hepatitis.
- Severe respiratory failure, circulatory collapse and severe arterial hyotension.
- Pregnancy and Lactation (see “Pregnancy and lactation”).

Warnings:

AMIODARONE 150MG/3ML OETHMAAN is considered unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in vitro* systems.

When the following medical problems exist, the risk-benefit should be considered:

- Congestive heart failure
- Hepatic function impairment (lower doses may be required)
- Hypokalaemia (should be corrected prior to initiation of AMIODARONE 150MG/3ML OETHMAAN therapy; AMIODARONE 150MG/3ML OETHMAAN may be ineffective of arrhythmogenic)
- Thyroid function impairment, including goiter or nodules (increased risk of hypothyroidism or hyperthyroidism)
- Caution is recommended also during open-heart surgery in patients receiving AMIODARONE 150MG/3ML OETHMAAN because of the risk of hypotension upon discontinuation of cardiopulmonary bypass.

AMIODARONE 150MG/3ML OETHMAAN should be administered solely in 5% dextrose since it is

incompatible with saline. Solutions containing less than 2 ampoules AMIODARONE 150MG/3ML OETHMAAN in 500ml 5 % dextrose are unstable and should not be used. Flexible PVC bags are not suitable for the preparation of infusion solutions containing amiodarone.

Interactions:
Note: AMIODARONE 150MG/3ML OETHMAAN may interact with other medications for weeks to months after it is discontinued because of its slow elimination.

Concomitant administration with arrhythmogenic drugs, for example phenothiazine antipsychotics, tricyclic antidepressants, halofantrine, and terfenadine, should be avoided. AMIODARONE 150MG/3ML OETHMAAN may produce additive cardiac effects with other antiarrhythmics and increase the risk of tachyarrhythmias; amiodarone increases plasma concentrations of quinidine, procainamide, flecainide, and phenytoin; concurrent use of amiodarone with quinidine, disopyramide, procainamide, or mexiletine has been reported to result in a more prolonged QT interval and, rarely, *torsades de pointes,* and therefore, concurrent use with all class 1 antiarrhythmics requires great caution.

Since AMIODARONE 150MG/3ML OETHMAAN inhibits metabolism and potentiates the anticoagulant effect, the effects of warfarin and other oral anticoagulants (coumarin-derivative) may be enhanced, beginning as early as 4 to 6 days after initiation of AMIODARONE 150MG/3ML OETHMAAN therapy and persisting as long as weeks or months after it is withdrawn; prothrombin times may double or triple, but effect is very erratic; it is recommended that the dose of anticoagulant be reduced by one third to one half and that the prothrombin times be monitored closely.

In patients with underlying sinus function impairment, the concomitant administration of AMIODARONE 150MG/3ML OETHMAAN with beta-adrenergic blocking agents and calcium channel blocking agents may cause potentiation of bradycardia, sinus arrest, and atrioventricular (AV) block.

AMIODARONE 150MG/3ML OETHMAAN increases serum concentrations of digoxin and probably other digitalis glycosides, possibly to toxic levels. This may produce additive effects on sinoatrial (SA) and AV nodes. Therefore, digitalis glycosides should be withdrawn or the dosage reduced by 50 %. If continued, digitalis

serum concentrations should be carefully monitored.
Concurrent use of AMIODARONE 150MG/3ML OETHMAAN with potassium depleting diuretics (loop/ thiazide diuretics/ indapamide) may lead to an increased risk of arrhythmias associated with hypokalaemia.
AMIODARONE 150MG/3ML OETHMAAN may increase plasma concentrations of phenytoin, resulting in increased adverse effects and/or toxicity.

Bradycardia unresponsive to AMIODARONE 150MG/3ML OETHMAAN and hypotension are the potentially severe complications that have been reported in patients taking amiodarone and undergoing general anaesthesia. Patients receiving AMIODARONE 150MG/3ML OETHMAAN should inform the anaesthetist.

Pregnancy and lactation:
Administration during pregnancy should be avoided since AMIODARONE 150MG/3ML OETHMAAN crosses the placenta and has the potential to cause the following adverse effects: bradycardia and effects on thyroid status (iodine is known to cause foetal goitre, hypothyroidism, and mental retardation) in the neonate.
AMIODARONE 150MG/3ML OETHMAAN is distributed into human breast milk. Use by breastfeeding mothers is not recommended and mothers should be advised to contact a doctor before nursing.

One ampoule of AMIODARONE 150MG/3ML OETHMAAN contains approximately 56 mg of iodine. Iodine freely crosses the placenta and may cause thyroid disorders in the foetus; the uncertainty as to the effect of this iodine load on the foetus has largely limited the use of amiodarone in pregnancy.

Dosage and directons for use:
AMIODARONE 150MG/3ML OETHMAAN should only be used when facilities for close monitoring of cardiac function and resuscitation are available.
It is given by intravenous infusion usually in a dose is 5mg /kg body weight in 250ml glucose 5 %, infused over 20 minutes to 2 hours; further doses may be given up to a maximum of 1200mg in up to 500ml of dextrose 5 %, in 24 hours. Repeated infusions are preferably made through a central venous catheter.
In emergencies it may be given in doses of 150mg to 300mg in 10 to 20ml of dextrose by slow intravenous injection over a period of not less than 3 minutes; a second injection should not be given until at least 15 minutes after the first.

Maintenance treatment:

The intravenous route is not intended for long-term (longer than 3 weeks) maintenance treatment. Patients may be switched to oral amiodarone, once their arrhythmias have been suppressed by intravenous AMIODARONE 150MG/3ML OETHMAAN. The optimal dose to use when changing from intravenous to oral amiodarone will depend on the dose of intravenous AMIODARONE 150MG/3ML OETHMAAN already administered, as well as the bioavailability of oral amiodarone.

Clinical monitoring is recommended, particularly in elderly patients who are changed to oral amiodarone therapy.

Side effects and special precautions:

Side effects:

Adverse effects are common with AMIODARONE 150MG/3ML OETHMAAN; many are dose-related and reversible with reduction in dose.

Cardiac disorders:

Severe bradycardia, sinus arrest, conduction disturbances.

Less frequent: Arrhythmias; congestive heart failure; sinus bradycardia.

Ventricular tachyarrhythmias; *torsade de pointes* appear to be less of a problem with AMIODARONE 150MG/3ML OETHMAAN than other antiarrhythmics.

Less frequently, heart failure may be precipitated or aggravated.

Endocrine disorders:

Less frequent: Hypothyroidism.

Hyperthyroidism.

AMIODARONE 150MG/3ML OETHMAAN is reported to reduce the peripheral transformation of thyroxine [levothyroxine] (T4) to tri-iodothyronine (T3) and to increase the formation of reverse-T3. It can affect thyroid function and may induce hypo- or hyperthyroidism.

Eye disorders:

Less frequent: ocular toxicity; including optic neuropathy and/or optic neuritis.

Prolonged treatment with AMIODARONE 150MG/3ML OETHMAAN causes the development of benign yellowish-brown corneal micro-deposits, but these are reversible on stopping therapy.

Gastro-intestinal disorders:

The following side effects have been reported but frequencies are unknown:

Nausea and vomiting.

General disorders and administration site conditions:

The following side effects have been reported but frequencies are unknown:

Sweating.

A metallic taste, and fatigue.

Hepatobiliary disorders:

The following side effects have been reported but frequencies are unknown:

Cirrhosis or hepatitis; fatalities have been reported.

In hepatitis, hepatic enzymes are commonly elevated to several times normal within 2 months after initiation of therapy; deaths as a result of hepatic failure resembling alcoholic cirrhosis have occurred rarely.

Investigations:

The following side effect has been reported but frequency is unknown:

There may be abnormal liver function tests.

Nervous system disorders:

Frequent: Neurotoxicity (trouble in walking; numbness or tingling in fingers or toes; trembling or shaking of hands; unusual and uncontrolled movements of the body; weakness of arms or legs). Other adverse effects reported include headaches, tremor, sleeplessness, peripheral neuropathy, paraesthesias and ataxia.

Psychiatric disorders:

The following side effect has been reported but frequency is unknown:

Nightmares.

Reproductive system and breast disorders:

Less frequent: Noninfectious epididymitis.

Respiratory, thoracic and mediastinal disorders:

Frequent: pulmonary fibrosis or interstitial pneumonitis / alveolitis.

Severe pulmonary toxicity including pulmonary fibrosis and interstitial pneumonitis. These effects are usually reversible on withdrawal of amiodarone but are potentially fatal.

Skin and subcutaneous tissue disorders:

Frequent: Photosensitivity reactions are also common, particularly to long-wave, ultraviolet-A [UVA] light.

Less frequent: Blue-grey discolouration of the skin.

Vascular disorders:

Frequent: Hypotension.

Severe hypotension may follow intravenous administration particularly, though not exclusively, at rapid infusion rates.

Hypotension can also be precipitated by overdosage.

Thrombophlebitis can occur if amiodarone is injected regularly or infused for prolonged periods into a peripheral vein. Rapid intravenous administration has been associated with anaphylactic shock and hot flushes.

Precautions:

Cardiac disorders:

AMIODARONE 150MG/3ML OETHMAAN should not be given to patients with bradycardia, sino-atrial block, atrioventricular block or other severe conduction disorders (unless the patient has a pacemaker), severe hypotension, or severe respiratory failure. It may be used with caution in patients with heart failure. Electrolyte

disorders should be corrected before starting treatment.

Endocrine disorders:

The use of AMIODARONE 150MG/3ML OETHMAAN should be avoided in patients with disorders of the thyroid gland, or with a history of thyroid disorders.

Investigations:

Thyroid function should be monitored regularly in order to detect AMIODARONE 150MG/3ML OETHMAAN induced hyper- or hypothyroidism. Tests of liver and pulmonary function also should be carried out regularly inpatients on long-term therapy.

General disorders and administration site conditions:

The use of AMIODARONE 150MG/3ML OETHMAAN should be avoided in patients with iodine sensitivity.
Patients taking AMIODARONE 150MG/3ML OETHMAAN should avoid exposure to sunlight.

Known symptoms of overdosage and particulars of its treatment:
Rapid administration or overdosage may precipitate circulatory collapse.
Treatment is primarily supportive and symptomatic.
It is important to monitor cardiac rhythm and blood pressure.
A beta-adrenergic agonist or pacemaker may be indicated for bradycardia. In such patients

presenting with bradycardia, the use of atropine has been successful.
Hypotension may respond to positive inotropic and/or vasopressor agents.

Identification:

Clear, colourless to pale yellow solution for intravenous administration.

Presentation:

Clear, colourless glass ampoules for intravenous injection containing 150mg amiodarone hydrochloride in 3 ml.

Packs of 10 X 3 ml ampoules.

Storage instructions:

Store below 25 °C. Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

Registration number:

A39/6.2/0156

Name and business address of the holder of the registration:

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