# PROFESSIONAL INFORMATION

## SCHEDULING STATUS

S4

## 1. NAME OF THE MEDICINE

**AMIODARONE IV ACTIVO** solution for injection.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml ampoule contains 150 mg amiodarone hydrochloride.

Excipients with known effect:

Preservative: Benzyl alcohol 2,02 % *w/v*

Sugar free

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear colourless or slightly yellowish solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

Cardiopulmonary resuscitation in the event of cardiac arrest in adults, caused by ventricular fibrillation resistant to external electric shock.

## 4.2 Posology and method of administration

AMIODARONE IV ACTIVO should only be used when facilities exist for cardiac monitoring or defibrillation, should the need arise (see section 4.4).

### Intravenous infusion

The standard recommended dose is 5 mg/kg body mass given by intravenous infusion over a period of 20 minutes to 2 hours. Where possible this should be administered as a dilute solution in 250 ml 5 % dextrose. This may be followed by repeat infusions up to 1 200 mg (approximately 15 mg/kg body mass) in up to 500 ml 5 % dextrose per 24 hours, the rate of infusion being adjusted on the basis of clinical response.

When given by infusion, AMIODARONE IV ACTIVO may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

### Intravenous injection

AMIODARONE IV ACTIVO may, at the discretion of the doctor, be given as a bolus injection of 150 – 300 mg in 10 – 20 ml over a minimum of 3 minutes. This should not be repeated for at least 15 minutes. Patients treated in this way must be closely monitored e.g. in an intensive care unit (see section 4.4).

### Cardiopulmonary resuscitation of shock resistant ventricular fibrillation

In the specific case of cardiopulmonary resuscitation of shock resistant ventricular fibrillation, a first dose of 300 mg diluted in 20 ml of 5 % dextrose solution (or 5 mg/kg of estimated body weight diluted in 30 ml of 5 % dextrose) AMIODARONE IV ACTIVO is administered via bolus IV injection. An additional 150 mg or 2,5 mg/kg IV dose may be considered if the ventricular fibrillation persists.

### Maintenance therapy

Oral therapy should be initiated concomitantly at the usual loading dose as soon as possible after an adequate response is obtained and the intravenous therapy gradually phased out. Repeated

or continuous infusion via peripheral veins may lead to local discomfort and inflammation. When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.

**Special populations**

*Elderly population*

It is important that the minimum effective dose is used. Whilst there is no-evidence that dosage requirements are different for this group of patients, they may be more susceptible to bradycardia and conduction defects if too high a dose is employed.

**Paediatric population**

The safety and efficacy of AMIODARONE IV ACTIVO in paediatric patients have not been established. Therefore, its use in paediatric patients is not recommended (see section 4.3).

**Method of administration**

Only 5 % dextrose should be used as diluent.

AMIODARONE IV ACTIVO, 150 mg/3 ml solution for injection is a concentrate that is administered by intravenous injection or infusion after dilution in 5 % dextrose.

Solutions containing less than 0,6 mg/ml of amiodarone in 5 % dextrose are unstable and should not be used. AMIODARONE IV ACTIVO is incompatible with saline and should be administered solely in 5 % dextrose.

Do not mix with other preparations in the same syringe. Do not inject other preparations in the same line.

**4.3 Contraindications**

- Hypersensitivity to iodine (as amiodarone contains iodine; one ampoule contains approximately 56 mg iodine) or to amiodarone, or to any of the excipients (see section 6.1).

- Sinus bradycardia and sinoatrial heart block and sick sinus syndrome (risk of sinus arrest), severe atrioventricular conduction disorders, unless a pacemaker is fitted.
- Bi- or tri-fascicular conduction disorders, unless a permanent functioning pacemaker is fitted or, unless the patient is in a special care unit and AMIODARONE IV ACTIVO is used under the cover of electro-systolic pacing.
- Combined therapy with medicines which may induce "*Torsades de Pointes*" (see section 4.5).
- Severe respiratory failure, circulatory collapse and severe arterial hypotension. Congestive heart failure is also a contraindication when using AMIODARONE IV ACTIVO as a bolus injection. Intravenous injection is contraindicated in case of hypotension, myocardiopathy or heart failure (possible worsening).
- Prophylactic use in the preoperative period of cardio-pulmonary surgery.
- Thyroid dysfunction (see section 4.4). Thyroid function tests should be performed where appropriate prior to therapy in all patients.
- Pregnancy (see section 4.6).
- Lactation (see section 4.6).

The above contraindications do not apply when AMIODARONE IV ACTIVO is used in the emergency treatment of cardiopulmonary resuscitation of shock (defibrillator) resistant ventricular fibrillation.

**Paediatric patients:** The safety and efficacy of AMIODARONE IV ACTIVO in paediatric patients have not been established. Therefore, its use in paediatric patients is not recommended. The ampoules of AMIODARONE IV ACTIVO injectable contain benzyl alcohol. There have been reports of fatal "gasping syndrome" in neonates (children less than one month of age) following the administration of intravenous solutions containing this preservative. Symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse.

## 4.4 Special warnings and precautions for use

*Porphyria*

Avoid use in patients with porphyria as it may precipitate an attack.

*Intravenous bolus injection*

Intravenous bolus injection is not advised because of haemodynamic risks (severe hypotension, circulatory collapse). Intravenous infusion is preferable whenever possible.

Intravenous bolus injection is to be done only in an emergency where alternative therapies have failed and only in a heart intensive care unit under continuous monitoring (ECG, blood pressure).

*Intravenous administration*

AMIODARONE IV ACTIVO should only be used in a special care unit under continuous monitoring (ECG, blood pressure). Repeated or continuous infusion via peripheral veins may lead to injection site reactions; AMIODARONE IV ACTIVO should, whenever possible, be administered through a central venous line.

When given by infusion AMIODARONE IV ACTIVO may reduce drop size and, if appropriate, adjustments should be made to the rate of infusion.

Dosage is approximately 5 mg/kg body-weight. Except for cases of cardiopulmonary resuscitation of shock resistant ventricular fibrillation, AMIODARONE IV ACTIVO should be injected over a minimum period of 3 minutes. Intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only one ampoule (possible irreversible collapse). Do not mix other preparations in the same syringe. Do not inject other preparations in the same line. Where the treatment should be continued, continue with intravenous infusion (see section 4.2).

*Cardiac disorders*

Onsets of new dysrhythmias or worsening of treated dysrhythmias sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the medicine from a pro-dysrhythmic effect, or whether it is a worsening of the cardiac condition. The pro-dysrhythmic effect of AMIODARONE IV ACTIVO has usually occurred in combination with precipitating factors, such as interactions particularly other antidysrhythmic medicines, digoxin and hypokalaemia and/or electrolyte disorders (see sections 4.5 and 4.8).

Latent or manifest heart failure may be worsened by AMIODARONE IV ACTIVO. In this case, AMIODARONE IV ACTIVO should be associated with the usual cardiotonic and diuretic treatments.

AMIODARONE IV ACTIVO may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digoxin therapy. In these circumstances AMIODARONE IV ACTIVO treatment should be withdrawn. If necessary, beta-adreno stimulants or glucagon may be given.

*Pulmonary disorders*

The onset of dyspnoea or non-productive cough may be related to pulmonary toxicity such as interstitial pneumonitis. Cases of interstitial pneumonitis have been reported with AMIODARONE IV ACTIVO. A chest x-ray should be performed when the diagnosis is suspected, in patients developing effort dyspnoea whether isolated, or associated with deterioration of general health status (fatigue, weight loss, fever). AMIODARONE IV ACTIVO therapy should be re-evaluated since interstitial pneumonitis may be reversible following early withdrawal of AMIODARONE IV ACTIVO (clinical signs usually resolving within 3 to 4 weeks, followed by slower radiological and lung pulmonary function improvement within several months), and corticosteroid therapy should be considered.

Cases of severe respiratory complications, sometimes fatal, have been observed usually in the period immediately following surgery (adult acute respiratory distress syndrome); a possible

interaction with a high oxygen concentration may be implicated (see Anaesthesia below and section 4.5).

*Hepatic disorders*

Acute liver disorders (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur with oral and intravenous forms and within the first 24 hours of AMIODARONE IV ACTIVO (see section 4.8).

*Hepatic monitoring*

It is advisable to monitor liver function, particularly transaminases, before treatment and periodically thereafter. Patients with abnormal liver function tests should be reassessed clinically and tests of liver function should be monitored closely until they return to normal.

If patients present with abnormal liver function tests, dosage reduction should be considered. If liver function test values continue to rise despite reduction in dosage or in situations where dosage reduction is not feasible, discontinuation of AMIODARONE IV ACTIVO should be considered. The patient's clinical condition should be carefully monitored both as regards the hepatic condition and control of the dysrhythmias.

*Endocrine disorders*

Both hyper- and hypothyroidism have occurred commonly during, or soon after, treatment with AMIODARONE IV ACTIVO (see section 4.8). Simple monitoring of the usual biochemical tests is confusing because some (PBI and $^{131}I$ uptake) are invalidated and others ($T_4$, $T_3$ and FTI) may be altered where the patient is clearly euthyroid. Clinical monitoring is therefore recommended and should be continued for some months after discontinuation of amiodarone treatment. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular testing is recommended.

Clinical features of hyperthyroidism such as mass loss, asthenia, restlessness, increase in heart rate or a recurrence of the cardiac dysrhythmia, angina or congestive heart failure, should alert

the doctor. The diagnosis may be supported by the finding of an elevated serum tri-iodothyronine ($T_3$), a low level of thyroid stimulating hormone (TSH as measured by high sensitivity methods) and a reduced TSH response to thyrotrophin releasing hormone (TRH). Elevation of reverse $T_3$ ($rT_3$) may also be found. The clinical features of hypothyroidism such as mass gain and reduced activity or excessive bradycardia should alert the doctor. The onset may be abrupt. The diagnosis may be supported by the presence of an elevated serum TSH level and an exaggerated TSH response to TRH. The thyroxine ($T_4$), $T_3$ and free thyroxine index (FTI) may be low.

In the case of hyperthyroidism AMIODARONE IV ACTIVO should be withdrawn.

Courses of anti-thyroid medication have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy may be required for several weeks.

Thyroid hypo-function usually resolves within 3 months of cessation of AMIODARONE IV ACTIVO; it may be treated cautiously with L-thyroxine. Concomitant use of AMIODARONE IV ACTIVO should only be used in life-threatening situations, when TSH levels may provide a guide to L-thyroxine dosage.

*Anaesthesia*

Before surgery, the anaesthetist should be informed that the patient is taking AMIODARONE IV ACTIVO (see section 4.5).

*Severe bradycardia and heart block*

Life-threatening cases of bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with AMIODARONE IV ACTIVO (see section 4.5).

Bradycardia has generally occurred within hours to days, but later cases have been mostly observed up to 2 weeks after initiating hepatitis C virus (HVC) treatment.

AMIODARONE IV ACTIVO should only be used in patients on sofosbuvir-containing regimen when other alternative anti-dysrhythmic treatments are not tolerated or are contraindicated.

Should concomitantly use of AMIODARONE IV ACTIVO be considered necessary, it is recommended that patients undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment.

Due to the long half-life of amiodarone as in AMIODARONE IV ACTIVO, cardiac monitoring as outlined above should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir-containing regimen.

All patients receiving AMIODARONE IV ACTIVO in combination with sofosbuvir-containing regimen should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them.

*Primary graft dysfunction (PGD) post cardiac transplant*

It is documented that amiodarone as in AMIODARONE IV ACTIVO use in the transplant recipient prior to heart transplant has been associated with an increased risk of PGD.

PGD is a life-threatening complication of heart transplantation that presents as a left, right or biventricular dysfunction occurring within the first 24 hours of transplant surgery for which there is no identifiable secondary cause (see section 4.8). Severe PGD may be irreversible.

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

*Severe bullous reactions*

Life-threatening or even fatal cutaneous reactions Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (see section 4.8). If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions)are present AMIODARONE IV ACTIVO treatment should be discontinued immediately.

*Eye disorders*

If blurred or decreased vision occurs (see section 4.8), complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic

neuritis requires AMIODARONE IV ACTIVO withdrawal due to the potential progression to blindness.

*Iodine*

AMIODARONE IV ACTIVO contains approximately 56 mg of iodine in a 3 ml ampoule. Iodine may interfere with radio-iodine uptake (see section 4.4).

*Benzyl alcohol*

AMIODARONE IV ACTIVO contains benzyl alcohol (2,02 % w/v) as a preservative. Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children under the age of 3 years old (see section 4.3: Paediatric patients).

**4.5 Interaction with other medicines and other forms of interaction**

Concomitant use of AMIODARONE IV ACTIVO is not recommended with the following medicines: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulating laxative which may cause hypokalaemia.

***Combinations which may induce "Torsades de Pointes"***

The risk of "*Torsades de Pointes*" may be increased when AMIODARONE IV ACTIVO is used in combination with other medicines which directly or indirectly prolong the QT interval.

*Combined therapy with medicines that may induce "Torsades de Pointes" is contraindicated (see section 4.3):*

- Antidysrhythmic medicines such as Class IA, sotalol, bepridil, disopyramide, quinidine.
- Non-antidysrhythmic medicines such as vincamine, some neuroleptic medicines, cisapride, erythromycin IV, pentamidine (when administered parenterally).
- Certain antihistamines such as astemizole, mizolastine.
- Antimalarials such as quinine, mefloquine, chloroquine, halofantrine.

- Lithium and tricyclic antidepressants e.g. doxepin, maprotiline, amitriptyline.
- Moxifloxacin.

***Combined therapy with the following medicines is not recommended:***

- Beta-blockers and heart rate lowering calcium channel inhibitors (verapamil, diltiazem) as automaticity (excessive bradycardia and conduction disorders may occur.
- Stimulating laxative medicines which may cause hypokalaemia such as senna and bisacodyl thus increasing the risk of "*Torsades de Pointes*"; other types of laxatives should be used.
- Fluoroquinolones should be avoided in patients receiving AMIODARONE IV ACTIVO. There have been reports of QTc interval prolongation, with or without "*Torsades de Pointes*", in patients taking amiodarone with fluoroquinolones.

***Caution should be exercised when using the following medicines in combination with AMIODARONE IV ACTIVO:***

*Medicines which induce hypokalaemia:*

- Diuretics inducing hypokalaemia, either alone or combined.
- Systemic corticosteroids (gluco-, mineralo-), tetracosactide.
- Amphotericin B.

It is necessary to prevent hypokalaemia (and to correct hypokalaemia); the QT interval should be monitored and, in case of "*Torsades de Pointes*", antidysrhythmic medicines should not be given (ventricular pacing should be initiated; IV magnesium may be used).

*Others:*

Concomitant administration with dysrhythmogenic medicines, for example phenothiazine antipsychotics, should be avoided. The effects of clonazepam may be enhanced by concomitant administration of AMIODARONE IV ACTIVO, and plasma concentrations of procainamide, and quinidine may be raised. Plasma AMIODARONE IV ACTIVO concentrations may be increased

by cimetidine and other inhibitors of metabolising enzymes CYP 3A4, including HIV-protease inhibitors.

***CYP2C9 substrates:***

*Oral anticoagulant:*

AMIODARONE IV ACTIVO raises the concentration of warfarin by inhibition of the cytochrome P450 2C9. The combination of warfarin with AMIODARONE IV ACTIVO may exacerbate the effect of the warfarin thus increasing the risk of bleeding. It is necessary to monitor prothrombin (INR) levels more regularly and to adjust oral doses of warfarin both during treatment with AMIODARONE IV ACTIVO and after discontinuation of AMIODARONE IV ACTIVO treatment.

*Phenytoin:*

Consideration should be given to the possibility that AMIODARONE IV ACTIVO may alter the plasma concentrations of other medication particularly those which are highly protein-bound e.g. phenytoin. AMIODARONE IV ACTIVO raises the plasma concentrations of phenytoin by inhibition of CYP 2C9. The combination of phenytoin and AMIODARONE IV ACTIVO may lead to phenytoin overdosage, resulting in neurological signs. Clinical monitoring should be undertaken and phenytoin dosage should be reduced if overdosage signs appear; phenytoin plasma levels may be determined when necessary. In addition, plasma AMIODARONE IV ACTIVO concentrations may be decreased by phenytoin.

***CYP2D6 substrates:***

*Flecainide:*

AMIODARONE IV ACTIVO raises plasma concentrations of flecainide by inhibition of the cytochrome CYP 2D6. Therefore, flecainide dosage should be adjusted accordingly and the patient closely monitored.

***PgP Substrates***

Amiodarone is a Pgp inhibitor. Co administration with Pgp substrates is expected to result in an increase in their exposure.

*Dabigatran:*

Caution should be exercised when amiodarone is co administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran as per its label.

*Digoxin:*

The plasma concentrations of digoxin may be raised with the concomitant administration of AMIODARONE IV ACTIVO. Administration of AMIODARONE IV ACTIVO to a patient already receiving digoxin may bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Monitoring is recommended and digoxin dosage should be adjusted accordingly. A synergistic effect on heart rate and atrioventricular conduction is also possible.

***Medicines metabolised by cytochrome P450 3A4:***

When such medicines are co-administered with AMIODARONE IV ACTIVO, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:

- Ciclosporin: its combination with AMIODARONE IV ACTIVO may increase ciclosporin plasma levels. Dosage should be adjusted.
- Fentanyl: its combination with AMIODARONE IV ACTIVO may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity.
- Other medicines metabolised by CYP 3A4: lidocaine (lignocaine), tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, simvastatin and other statins metabolised by CYP 3A4 (increased risk of muscular toxicity).
- Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral amiodarone.

***Anaesthesia:***

Potentially severe complications have been reported in patients receiving AMIODARONE IV ACTIVO, undergoing general anaesthesia: bradycardia (unresponsive to atropine), hypotension, disturbances of conduction, decreased cardiac output. 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 (see section 4.4).

***Other medicine interactions:***

Coadministration of amiodarone with sofosbuvir-containing regimens may lead to serious symptomatic bradycardia. The mechanism for this bradycardia effect is unknown. If coadministration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

In view of amiodarone's effect on the foetal thyroid gland, AMIODARONE IV ACTIVO is contraindicated during pregnancy. AMIODARONE IV ACTIVO should only be considered in pregnancy if no alternate therapy is available and dysrhythmias are life-threatening. Under these circumstances the mother/parent(s) should be counselled regarding harmful effects of AMIODARONE IV ACTIVO on the foetus, and written consent given thereto (see section 4.3).

**Breastfeeding**

Amiodarone is excreted into the breast milk in significant quantities and breastfeeding is contraindicated (see section 4.3).

**4.7 Effects on ability to drive and use machines**

Not relevant.

**4.8 Undesirable effects**

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent | Haemolytic anaemia, thrombocytopenia |
| | Frequency unknown | Neutropenia, agranulocytosis |
| Immune system disorders | Less frequent | Anaphylactic shock |
| | Frequency unknown | Angioedema, angioneurotic oedema (Quincke's Oedema) |
| Endocrine disorders | Frequent | Hypothyroidism and hyperthyroidism |
| | Less frequent | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) |
| Psychiatric disorders | Less frequent | Confusional state/delirium |
| Nervous system disorders | Less frequent | Benign intracranial hypertension, nightmares, headaches, vertigo, sleeplessness |
| Eye disorders | Frequency unknown | Optic neuropathy, neuritis, blindness |
| Cardiac disorders | Frequent | Bradycardia, generally moderate |
| | Less frequent | Conduction disturbances (sinoatrial block, AV block) |
| | Frequency unknown | *Torsade de pointes* |
| Vascular disorders | Frequent | Hypotension |
| | Less frequent | Hot flushes |

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders | Less frequent | Interstitial pneumonitis or fibrosis, adult acute respiratory distress syndrome, bronchospasm, apnoea |
| Gastrointestinal disorders | Less frequent | Nausea, vomiting, metallic taste, pancreatitis/acute pancreatitis |
| Hepato-biliary disorders | Less frequent | Increased serum transaminases, acute liver disorder, jaundice, hepatic failure |
| Skin and subcutaneous tissue disorders | Frequent | Eczema |
| | Less frequent | Sweating |
| | Frequency unknown | Urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, bullous dermatitis |
| Musculoskeletal, connective tissue and bone disorders | Frequency unknown | Back pain |
| Reproductive system and breast disorders | Frequency unknown | Libido decreased |
| General disorders and administrative site conditions | Frequent | Injection site reactions such as pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes |
| Injury, poisoning and procedural complaints | Frequency unknown | Primary graft dysfunction post cardiac transplant |

**Description of selective adverse reactions**

*Bradycardia,* generally moderate and dose-related. ECG changes, i.e. QT interval lengthening corresponding to prolonged repolarisation; U-waves and deformed T-waves may occur.
Conduction disturbances (sinoatrial block, AV block of various degrees) marked by bradycardia or sinus arrest in patients with sinus node dysfunction and or elderly patients. Onset of new dysrhythmia or worsening of existing dysrhythmia, sometimes followed by cardiac arrest.

*Vascular disorders:* Decrease in blood pressure was usually moderate and transient. Cases of hypotension or collapse have been reported following overdosage or a too rapid injection.

*Severe respiratory complications* (adult acute respiratory distress syndrome) is sometimes fatal. Bronchospasm and/or apnoea is reported in case of severe respiratory failure, and especially in asthmatic patients.

*Liver disorders:* Isolated increases in serum transaminases, which is usually moderate (1,5 to 3 times normal range) occurred at the beginning of therapy. It may return to normal with dose reduction or even spontaneously.
Acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, were reported and were sometimes fatal (see section 4.4).

*Skin disorders:* Severe skin reactions sometimes fatal including toxic epidermal necrolysis/Stevens-Johnson syndrome, bullous dermatitis and Medicine Reaction with Eosinophilia and Systematic Symptoms were reported.

*Injection site disorders:* Local inflammation of veins following intravenous infusion may be avoided by the use of a central venous catheter.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

**4.9 Overdose**

Circulatory collapse may be precipitated by too rapid an administration or overdosage. Atropine has been used successfully in such patients presenting with bradycardia.

Overdosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances AMIODARONE IV ACTIVO treatment should be withdrawn. In the event of an overdose general supportive measures should be employed. The patient should be monitored and if bradycardia ensues, beta-adreno stimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of AMIODARONE IV ACTIVO, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological classification: A 6.2 Cardiac depressants.

Pharmacotherapeutic group: Antiarrhythmics, class III.

ATC code: C01BD01.

**Mechanism of action**

Amiodarone is used for the treatment of tachydysrhythmias and has complex pharmacological actions.

Electrophysiological studies demonstrated that 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. The conduction rate is reduced in the atria, AV node and accessory pathways. Amiodarone also demonstrates non-competitive alpha and beta adrenoreceptor antagonism.

## 5.2 Pharmacokinetic properties

### Distribution

The average bioavailability of amiodarone is about 50 %, but varies widely. It is extensively distributed to body tissues and accumulates in fat as well as in skeletal muscles and highly perfused tissues such as liver, lungs, and spleen.

Amiodarone has been reported to be about 96 % bound to plasma proteins. The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy a pharmacological effect is evident for a month or more.

Amiodarone and desethylamiodarone are reported to cross the placenta and to be distributed into breast milk.

### Biotransformation

A major metabolite, desethylamiodarone, has antidysrhythmic properties.

### Elimination

There is very little urinary excretion of amiodarone or its metabolites, the major route of excretion being in faeces via the bile; some enterohepatic recycling may occur.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Benzyl alcohol

Polysorbate 80

Hydrochloric acid 10 % (pH adjustment)

Sodium hydroxide 10 % (pH adjustment)

Water for Injections.

### 6.2 Incompatibilities

Only 5 % dextrose should be used.

AMIODARONE IV ACTIVO is incompatible with saline and should be administered only with 5 % dextrose.

Solution containing less than 0,6 mg/ml of amiodarone in 5 % dextrose are unstable and should not be used.

### 6.3 Shelf life

3 years.

Reconstituted solution with Dextrose 5 % is stable for 12 hours.

### 6.4 Special precautions for storage

Store at or below 30 °C.

Store in original packaging.

### 6.5 Nature and contents of container

AMIODARONE IV ACTIVO 150 mg/3 ml solution for injection is packed in type I, amber neutral glass ampoules.

The ampoules are packed in an outer carton as packs of 5’s.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd.

Block B, Arena Office Park

272 West Avenue

Centurion

0157

## 8. REGISTRATION NUMBER(S)

*To be allocated.*

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

*To be allocated.*

## 10. DATE OF REVISION OF THE TEXT