SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT

Amiodarone Hydrochloride 200 mg Tablets

2  QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: amiodarone hydrochloride 200 mg

Excipient with known effect:
Each tablet also contains 100 mg lactose.

For the full list of excipients, see section 6.1

3  PHARMACEUTICAL FORM

Tablets.

White biconvex uncoated tablets marked ‘AM’ breakline ‘200’ on one side and ‘G’ on the reverse.
The tablet can be divided into equal doses.

4  CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment should be initiated and normally monitored only under hospital or specialist supervision.

Amiodarone is indicated only for the treatment of serious and/or symptomatic rhythm disorders not responding to other therapies or when other treatments cannot be used.

Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.

Atrial flutter and fibrillation when other drugs cannot be used.

All types of tachyarrhythmias of paroxysmal nature, including: supraventricular, nodal and ventricular tachycardias, ventricular fibrillation when other drugs cannot be used.

Tablets are used for stabilisation and long term treatment
Amiodarone is indicated for the prevention of ventricular arrhythmias in high-risk patients following myocardial infarction or in patients with clinical signs of congestive cardiac failure and/or LVEF less than 40% who are receiving appropriate cardiac failure treatment which includes ACE-inhibitors. The minimum effective dose must be used and treatment must be initiated and used only under hospital/specialist supervision.

4.2 Posology and method of administration

Amiodarone 200mg Tablets are for oral administration.

General considerations

Initial dosing
A high initial dose is necessary because of the slow onset of action whilst the necessary tissue levels of amiodarone are achieved.

Maintenance
Too high a dosage during maintenance therapy can lead to side effects which are believed to be related to high tissue levels of amiodarone and its metabolites.

Amiodarone is strongly protein bound and has an average plasma half life of 50 days (reported range 20-100 days). It follows that sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dosage. In patients with potentially lethal arrhythmias the long half-life is a valuable safeguard, as omission of occasional doses does not significantly influence the overall therapeutic effect. It is particularly important that the minimum effective dosage is used and the patient is monitored regularly to detect the clinical features of excess amiodarone dosage. Therapy may then be adjusted accordingly.

Dosage reduction/withdrawal
Side effects slowly disappear as tissue levels fall. Following drug withdrawal, residual tissue-bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of cardiac arrhythmias during this period should be considered.

Because of the effect of food on absorption, amiodarone should be taken at a consistent time with respect to meals (see section 5.2).

Adults
It is particularly important that the minimum effective dose is used in all cases and that dosage is judged on the patient’s individual response and well-being. The following dosage schedules are generally effective:

Initial stabilisation
Treatment should be started with 200 mg, 3 times a day and may continue for 1 week. The dosage should then be reduced to 200 mg, twice daily for a further week.

Maintenance
After the initial period, the dosage should be reduced to a single 200 mg daily dose, or a lower dose if appropriate. The 100 mg tablets may be used to establish the minimum daily dose required to maintain control of the arrhythmia. On rare occasions the maintenance dose may
exceed 200 mg. The maintenance dose should be reviewed regularly, especially if it exceeds 200 mg.

*Change over from intravenous to oral therapy*
As soon as an adequate response has been obtained, oral therapy should be initiated concomitantly at the usual loading dose (200 mg three times a day). Intravenous amiodarone should then be phased out gradually.

In patients taking amiodarone concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day. (See sections 4.4 and 4.5)

*Elderly*
As with all patients, it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for the elderly, they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. The monitoring of thyroid function should be paid particular attention (see sections 4.3, 4.4 and 4.8).

*Paediatric population*
The safety and efficacy of amiodarone in children has not been established. Therefore, its use in paediatric patients is not recommended. Currently available data are described in sections 5.1 and 5.2 but no recommendations on posology can be made.

### 4.3 Contraindications

Sinus bradycardia and sino-atrial heart block. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block), or sinus node disease, amiodarone should only be used in conjunction with a pacemaker.

Evidence or history of thyroid dysfunction. Thyroid function tests should be performed in all patients prior to therapy with amiodarone.

Hypersensitivity to amiodarone or to any of the excipients listed in section 6.1 or to iodine. One 200 mg tablet contains approximately 75 mg iodine.

The combination of amiodarone with drugs which may induce torsades de pointes is contra-indicated (see section 4.5).

Concomitant treatment with monoamine oxidase inhibitors is contraindicated.

Pregnancy, except in exceptional circumstances (see section 4.6)

Lactation (see section 4.6)

### 4.4 Special warnings and precautions for use

As this product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system (see section 4.8). Because these reactions may be delayed, patients on long-term treatment should be carefully supervised. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given.

Before surgery, the anaesthetist should be informed that the patient is taking amiodarone (see sections 4.5 and 4.8).

**Cardiac disorders (see section 4.8)**

Too high a dosage 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 treatment should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

Oral amiodarone is not contraindicated in patients with latent or manifest heart failure, but caution should be exercised as, occasionally, existing heart failure may be worsened. In such cases, amiodarone tablets may be used with other appropriate therapies.

The pharmacological action of amiodarone induces ECG changes: QT prolongation (related to prolonged repolarisation) with the possible development of U-waves and deformed T-waves; these changes do not reflect toxicity.

In the elderly, heart rate may decrease markedly.

Treatment should be discontinued in case of onset of second or third degree AV-block, sino-atrial block or bifascicular block (see also section 4.3).

Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the drug from a pro-arrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Pro-arrhythmic effects generally occur in the context of QT prolonging factors such as drug interactions and/or electrolytic disorders (also see sections 4.5 and 4.8). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.

Before starting amiodarone, it is recommended to perform an ECG and serum potassium measurement. Monitoring of ECG is recommended during treatment.

Amiodarone may increase the defibrillation threshold and/or pacing threshold in patients with an implantable cardioverter defibrillator or a pacemaker, which may adversely affect the efficacy of the device. Regular tests are recommended to ensure the proper function of the device after initiation of treatment or change in posology.

Severe bradycardia (see section 4.5)

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when amiodarone is used in combination with sofosbuvir in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir or ledipasvir. Therefore, coadministration of these agents with amiodarone is not recommended.

If concomitant use with amiodarone cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir in combination with other DAAAs. Patients who are identified as being at high risk of bradyarrhythmia should be continuously monitored for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.
Patients receiving these hepatitis C medicines with amiodarone, with or without other medicines that lower heart rate, should be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they experience them.

**Endocrine disorders (see section 4.8)**
Amiodarone may induce hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders. Clinical and biological [including ultrasensitive TSH (usTSH)] monitoring should be performed prior to therapy in all patients. Monitoring should be carried out during treatment, at six-monthly intervals, and for several months following its discontinuation. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular assessment is recommended. Serum usTSH level should be measured when thyroid dysfunction is suspected.

Amiodarone contains iodine and thus may interfere with radio-iodine uptake. However, thyroid function tests (free-T3, free-T4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T4) to triiodothyronine (T3) and may cause isolated biochemical changes (increase in serum free-T4, free-T3 being slightly decreased or even normal) in clinically euthyroid patients. There is no reason in such cases to discontinue amiodarone treatment if there is no clinical or further biological (usTSH) evidence of thyroid disease.

**Hypothyroidism**
Hypothyroidism should be suspected if the following clinical signs occur: weight gain, cold intolerance, reduced activity, excessive bradycardia. The diagnosis is supported by an increase in serum usTSH and an exaggerated TSH response to TRH. T3 and T4 levels may be low. Euthyroidism is usually obtained within 3 months following the discontinuation of treatment. In life-threatening situations, amiodarone therapy can be continued, in combination with levothyroxine. The dose of levothyroxine is adjusted according to TSH levels.

**Hyperthyroidism**
Hyperthyroidism may occur during amiodarone treatment, or up to several months after discontinuation. Clinical features such as weight loss, asthenia, restlessness, increase in heart rate, onset of arrhythmia, angina, congestive heart failure should alert the physician. The diagnosis is supported by decrease in serum usTSH level, an elevated T3 and a reduced TSH response to thyrotropin releasing hormone. Elevation of reverse T3 (rT3) may also be found.

In the case of hyperthyroidism, amiodarone should be withdrawn. Clinical recovery usually occurs within a few months, although severe cases, sometimes resulting in fatalities, have been reported. Clinical recovery precedes the normalisation of thyroid function tests.

Courses of anti-thyroid drugs 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 (e.g. 1 mg/kg prednisolone) may be required for several weeks.

**Eye disorders (see section 4.8)**
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness. Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually.

**Hepatobiliary disorders (see section 4.8)**
Amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. Some fatalities have been reported, mainly following long-term
therapy, although rarely they have occurred soon after starting treatment, particularly when administered intravenously. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter. Amiodarone dose should be reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range.

At the beginning of therapy, elevation of serum transaminases which can be in isolation (1.5 to 3 times normal) may occur. These may return to normal with dose reduction, or sometimes spontaneously.

Isolated cases of acute liver disorders with elevated serum transaminases and/or jaundice may occur. In such cases treatment should be discontinued.

There have been reports of chronic liver disease. Alteration of laboratory tests which may be minimal (transaminases elevated 1.5 to 5 times normal) or clinical signs (possible hepatomegaly) during treatment for longer than 6 months should suggest this diagnosis. Routine monitoring of liver function tests is therefore advised. Abnormal clinical and laboratory test results usually regress upon cessation of treatment, but fatal cases have been reported. Histological findings may resemble pseudo-alcoholic hepatitis, but they can be variable and include cirrhosis.

Although there have been no literature reports on the potentiation of hepatic adverse effects of alcohol, patients should be advised to moderate their alcohol intake while taking amiodarone tablets.

Nervous system disorders (see section 4.8)
Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy. Both these conditions may be severe, although recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete.

Respiratory, thoracic and mediastinal disorders (See section 4.8)
Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonitis). Presenting features can include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough and deterioration in general health (fatigue, weight loss and fever). The onset is usually slow but may be rapidly progressive. Whilst the majority of cases have been reported with long term therapy, a few have occurred soon after starting treatment.

Patients should be carefully evaluated clinically and consideration given to chest X-rays before starting therapy. During treatment, if pulmonary toxicity is suspected, this should be repeated and associated with lung function testing including, where possible, measurement of transfer factor. Initial radiological changes may be difficult to distinguish from pulmonary venous congestion. Pulmonary toxicity has usually been reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy. Clinical symptoms often resolve within a few weeks followed by slower radiological and lung function improvement. Some patients can deteriorate despite discontinuing amiodarone.

Skin and subcutaneous tissue disorders (see section 4.8)
Patients should be instructed to avoid exposure to sun and to use protective measures during therapy as patients taking amiodarone tablets can become unduly sensitive to sunlight, which may persist after several months of discontinuation of amiodarone. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen (see section 4.8).
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 treatment should be discontinued immediately.

Drug interactions (see section 4.5)
Concomitant use of amiodarone is not recommended with the following drugs: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulant laxative agents which may cause hypokalaemia.

Increased plasma levels of flecainide have been reported with co-administration of amiodarone. The flecainide dose should be reduced accordingly and the patient closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Some of the more important drugs that interact with amiodarone include warfarin, digoxin, phenytoin and any drug which prolongs the QT interval.

Pharmacodynamic interactions

Drugs inducing Torsade de Pointes or prolonging QT

Drugs inducing Torsade de Pointes
Combined therapy with the following drugs which prolong the QT interval is contra-indicated (see section 4.3) due to the increased risk of torsades de pointes; for example:

- Class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide.
- Class III anti-arrhythmic drugs e.g. sotalol, bretylium.
- intravenous erythromycin, co-trimoxazole or pentamidine injection.
- some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride and sertindole.
- lithium and tricyclic anti-depressants, e.g. doxepin, maprotiline, amitriptyline.
- certain antihistamines, e.g. terfenadine, astemizole, mizolastine.
- anti-malarials, e.g. quinine, mefloquine, chloroquine, halofantrine.
- moxifloxacin.

Drugs prolonging QT interval

Co-administration of amiodarone with drugs known to prolong the QT interval (such as clarithromycin) must be based on a careful assessment of the potential risks and benefits for each patient since the risk of torsade de pointes may increase and patients should be monitored for QT prolongation.

There have been rare reports of QTc interval prolongation, with or without torsades de pointes, in patients taking amiodarone with fluoroquinolones. Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contraindicated, see section 4.3).

Drugs lowering heart rate or causing automaticity or conduction disorders

Combined therapy with the following drugs is not recommended:
• beta blockers and heart-rate lowering calcium channel inhibitors (diltiazem, verapamil, bepridil); potentiation of negative chronotropic properties and conduction slowing effects may occur.

Agents which may induce hypokalaemia

Combined therapy with the following drugs is not recommended:
• stimulant laxatives, which may cause hypokalaemia thus increasing the risk of torsades de pointes; other types of laxatives should be used.

Caution should be exercised over combined therapy with the following drugs which may also cause hypokalaemia and/or hypomagnesaemia, e.g. diuretics, systemic corticosteroids, tetracosactide, intravenous amphotericin.

In cases of hypokalaemia, corrective action should be taken and QT interval monitored. In case of torsades de pointes anti-arrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.

General anaesthesia
Caution is advised in patients undergoing general anaesthesia, or receiving high dose oxygen therapy.

Potentially severe complications have been reported in patients taking amiodarone undergoing general anaesthesia: bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output.

A few cases of adult respiratory distress syndrome, sometime fatal most often in the period immediately after surgery, have been observed. A possible interaction with a high oxygen concentration may be implicated.

Effect of amiodarone on other medicinal products
Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.

Due to the long half-life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone

PgP substrates
Amiodarone is a P-gp inhibitor. Co-administration with P-gp substrates is expected to result in an increase of their exposure.

Digitalis
Administration of amiodarone tablets to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Clinical, ECG and biological monitoring is recommended and digoxin dosage should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.

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.
CYP2C9 substrates
Amiodarone raises the plasma concentrations of oral anticoagulants (warfarin) and phenytoin by inhibition of CYP2C9.

-Warfarin
The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended.

-Phenytoin
Phenytoin dosage should be reduced if signs of overdosage appear (resulting in neurological signs), and plasma levels may be measured.

CYP P450 3A4 substrates
When such drugs are co-administered with amiodarone, an inhibitor of CYP 3A4, this may result in a higher level of their plasma concentration, which may lead to a possible increase in their toxicity:

- Ciclosporin: plasma levels of ciclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of ciclosporin may be necessary to maintain the plasma concentration within the therapeutic range.
- Statins: the risk of muscular toxicity is increased by concomitant administration of amiodarone with statins metabolised by CYP3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolized by CYP3A4 when given with amiodarone.
- Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine ergotamine and colchicine.

CYP 2D6 substrates
Flecainide
Given that flecainide is mainly metabolised by CYP 2D6, by inhibiting this isoenzyme, amiodarone may increase flecainide plasma levels; it is advised to reduce the flecainide dose by 50% and to monitor the patient closely for adverse effects. Monitoring of flecainide plasma levels is strongly recommended in such circumstances (see section 4.4).

Effect of other medicinal products on amiodarone
CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit amiodarone metabolism and to increase its exposure.

It is recommended to avoid CYP3A4 inhibitors during treatment with amiodarone.

Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral amiodarone.

Other drug interactions with amiodarone (see section 4.4)
Coadministration of amiodarone with sofosbuvir in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) is not recommended as it 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
There are insufficient data on the use of amiodarone during pregnancy in humans to judge any possible toxicity. However, in view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances. If, because of the long half-life of amiodarone, discontinuation of the drug is considered prior to planned conception, the real risk of recurrence of life threatening arrhythmias should be weighed against the possible hazard for the foetus.

No teratogenic effects have been observed in animals and there is insufficient data on the use of amiodarone during pregnancy to confirm any possible toxicity.

Breast-feeding
Contraindicated during breast-feeding as amiodarone is present in breast milk in sufficient quantity to affect the child adversely.

Fertility
Elevated serum levels of LH and FSH were found in male patients after long-term treatment indicating testicular dysfunctions.

4.7  Effects on ability to drive and use machines

The ability to drive or to operate machinery may be impaired in patients with clinical symptoms of amiodarone-induced eye disorders.

4.8  Undesirable effects

The following adverse reactions are classified below by system organ class and ranked under heading of frequency using the following convention: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

| Very rare: | Haemolytic anaemia, aplastic anaemia and thrombocytopenia. |
|           | In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown. |

Immune system disorders

| Not known: | Angioedema. Anaphylactic reaction, anaphylactic shock. |

Endocrine disorders (see section 4.4)
**Common:** Hyperthyroidism, sometimes fatal.
Hypothyroidism.

**Very rare:** Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

**Metabolism and nutrition disorders**

**Not known:** Decreased appetite.

**Psychiatric disorders**

**Not known:** Confusional state/delirium.

**Nervous system disorders**

**Common:** Extrapyramidal tremor, for which regression usually occurs after reduction of dose or withdrawal.
Nightmares, sleep disorders.

**Uncommon:** Peripheral sensorimotor neuropathy and/or myopathy, usually reversible on withdrawal of the drug (see section 4.4).

**Very rare:** Vertigo and headache.
Cerebellar ataxia for which regression usually occurs after reduction of dose or withdrawal.
Benign raised intracranial hypertension (pseudo-tumour cerebri).

**Not known:** Parkinsonism, parosmia.

**Eye disorders**

**Very common:** Corneal microdeposits usually limited to the area under the pupil, which are usually only discernible by slit-lamp examinations. They may be associated with coloured halos in dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment. The deposits are considered essentially benign and do not require discontinuation of amiodarone.

**Very rare:** Optic neuropathy/neuritis (that may lead to blindness) (see section 4.4).

**Cardiac disorders**

**Common:** Bradycardia, generally moderate and dose related.

**Uncommon:** Amiodarone has a low pro-arrhythmic effect.
Onset or worsening of arrhythmia, sometimes followed by cardiac arrest (see sections 4.4 and 4.5).
Conduction disturbances (sinoatrial block, AV block of various degrees) (see section 4.4).

**Very rare:** Marked bradycardia or sinus arrest in patients with sinus node dysfunction and/or in elderly patients.

**Not known:** Torsades de pointes (see sections 4.4 and 4.5).
**Vascular disorders**

**Very rare:** Vasculitis.

**Respiratory, thoracic and mediastinal disorders**

**Common:** Pulmonary toxicity (hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia BOOP). Sometimes this toxicity can be fatal (see section 4.4).

**Very rare:** Surgery (possible interaction with a high oxygen concentration, see sections 4.4 and 4.5). Bronchospasm in patients with severe respiratory failure and especially in asthmatic patients.

**Not known:** Pulmonary haemorrhage (there have been some reports of pulmonary haemorrhage, although exact frequencies are not known).

**Gastrointestinal disorders**

**Very common:** Benign gastrointestinal disorders (nausea, vomiting, dysgeusia) usually occurring with loading dosage and resolving with dose reduction.

**Common:** Constipation.

**Uncommon:** Dry mouth.

**Not known:** Pancreatitis/acute pancreatitis.

**Hepatobiliary disorders (see section 4.4)**

**Very common:** Isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times the normal range), occurring at the beginning of therapy. It may return to normal with dose reduction or even spontaneously.

**Common:** Acute liver disorders with high serum transaminases and/or jaundice, including hepatic failure, which are sometimes fatal.

**Very rare:** Chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal.

**Skin and subcutaneous tissue disorders**

**Very common:** Photosensitivity (see section 4.4).

**Common:** Slate grey or bluish discolouration of light exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation. Eczema.
Very rare: Exfoliative dermatitis and alopecia. Erythema during the course of radiotherapy. Skin rashes, usually non-specific.

Not known: Urticaria. Severe skin reactions sometimes fatal including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), bullous dermatitis, Drug reaction with eosinophilia and systematic symptoms (DRESS).

Musculoskeletal and connective tissue disorders
Not known: Lupus-like syndrome.

Reproductive system and breast disorders
Very rare: Epididymo-orchitis. Impotence.

General disorders and administration site conditions
Not known: Granuloma, including bone marrow granuloma.

Investigations
Very rare: Increase in blood creatinine.

Other
Metallic taste (which usually occurs with loading dosage and regresses on dose reduction).
Systemic Lupus Erythematosus.

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 [to be completed nationally with the national reporting system].

4.9 Overdose

Little information is available regarding acute overdosage with amiodarone. Few cases of sinus bradycardia, heart block, attacks of ventricular tachycardia, torsades de pointes, circulatory failure and hepatic injury have been reported.

In the event of overdose, treatment should be symptomatic; gastric lavage may be employed to reduce absorption in addition to general supportive measures. The patient should be monitored and if bradycardia occurs β-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur.

Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended. Neither amiodarone nor its metabolites are dialysable.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: C01B D01 Antiarrhythmics, class III

Amiodarone is a class III antiarrhythmic agent, prolonging the action potential duration in both atrial and ventricular myocardium. In addition it possesses weak non-competitive sympathetic adrenergic blocking properties. Class III antiarrhythmic effects are probably heterogeneous. They are, in general, associated with prolongation of the duration of the action potential and corresponding prolongation of the refractoriness of myocardial tissues. In the case of amiodarone, the prolongation of action potential duration is more uniform than other Class III Antiarrhythmic drugs.

A local tissue action, involving thyroid hormones and iodine content may be relevant, as analogues containing other halides do not show antiarrhythmic effects.

Paediatric population

No controlled paediatric studies have been undertaken.

In published studies the safety of amiodarone was evaluated in 1118 paediatric patients with various arrhythmias. The following doses were used in paediatric clinical trials.

**Oral**
- Loading dose: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m 2/day if expressed per square meter)
- Maintenance dose: the minimum effective dosage should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250 mg/m2/day if expressed per square meter)

**Intravenous**
- Loading dose: 5 mg/kg body weight over 20 minutes to 2 hours,
- Maintenance dose: 10 to 15 mg/kg/day from few hours to several days
If needed oral therapy may be initiated concomitantly at the usual loading dose.

5.2 Pharmacokinetic properties

Amiodarone is strongly protein bound and the plasma half life is usually of the order of 50 days. However there may be considerable interpatient variation; in individual patients a half life of less than 20 days and a half life of more than 100 days has been reported. High doses of amiodarone, for example 600mg/day, should be given initially to achieve effective tissue levels as rapidly as possible. Owing to the long half life of the drug, a maintenance dose of only 200mg/day, or less is usually necessary. Sufficient time must be allowed for a new distribution equilibrium to be achieved between adjustments of dose.

The long half life is a valuable safeguard for patients with potentially lethal arrhythmias as omission of occasional doses does not significantly influence the protection afforded by amiodarone.
No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

Amiodarone is metabolised mainly by CYP3A4, and also by CYP2C8. Amiodarone and its metabolite, desethylamiodarone, exhibit a potential in vitro to inhibit CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2A6, CYP2B6 and 2C8. Amiodarone and desethylamiodarone have also a potential to inhibit some transporters such as Pgp and organic cation transporter (OCT2) (One study shows a 1.1% increase in concentration of creatine (a OCT 2 substrate). In vivo data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and Pgp substrates.

5.3 Preclinical safety data

Preclinical findings of relevance to the prescriber have already been addressed in other parts of this document.

In a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen. These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings to man is low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose  
Cellulose, microcrystalline  
Povidone K30  
Crospovidone  
Silica, colloidal anhydrous  
Talc  
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.  
Blister: Store in the original package in order to protect from light and moisture.  
Container: Keep container tightly closed in order to protect from light and moisture.
6.5 Nature and contents of container

PVC/Aluminium foil blister strips or polypropylene containers fitted with polyethylene caps in pack sizes of 10, 20, 28, 30, 50, 60 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Herts
EN6 1TL

8. MARKETING AUTHORISATION NUMBER

PL 04569/0242

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/11/2006

10 DATE OF REVISION OF THE TEXT

09/08/2018