Summary of Product Characteristics

1. Name of the medicinal product
ZADARON 200mg Tablets

2. Qualitative and quantitative composition
Each tablet contains 200mg amiodarone hydrochloride.
For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablets.

4. Clinical particulars
4.1 Therapeutic indications

ZADARON is indicated only for the treatment of severe rhythm disorders not responding to other therapies or when other treatments cannot be used. Treatment should be initiated and normally monitored only under hospital or specialist supervision.
Atrial flutter and fibrillation when other drugs cannot be used.
All types of tachyarrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardias and ventricular fibrillation when other drugs cannot be used.
Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome.

4.2 Posology and method of administration

Adults
It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual's response and well-being.
The following dosage regimen is generally effective.
Initial Stabilisation
Treatment should be started with 200mg, 3 times a day and may be continued for 1 week. The dosage should then be reduced to 200mg, twice daily, for a further week.
Maintenance
After the initial period the dosage should be reduced to 200mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose. The scored 100mg tablet should be used to titrate the minimum dose required to maintain control of the arrhythmia. The Maintenance dosage should be regularly reviewed, especially where this exceeds 200mg daily.
General Considerations
Initial dosing
A high dose is needed in order to achieve adequate tissue levels rapidly.
Maintenance
It is particularly important that the minimum effective dosage is used and the patient is monitored regularly to detect clinical signs of excess amiodarone dosage. Therapy may then be adjusted accordingly. Side effects can result from too high a dose during maintenance therapy which are believed to be related to high tissue levels of amiodarone and its metabolites.
Sufficient time must be allowed for a new distribution equilibrium to be achieved between dosage adjustments. Amiodarone is strongly protein-bound and has an average plasma half-life of 50 days reported range 20-100 days). In patients with potential lethal arrhythmias the long-life is a valuable safeguard, as omission of occasional doses does not significantly influence the overall therapeutic effect.
It is particularly important 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.
Changeover from Intravenous to Oral Therapy
If patients are being switched from intravenous Amiodarone therapy, oral administration should be initiated concomitantly at the usual loading dose (200mg, 3 times a day) and then intravenous therapy gradually phased out.
Dosage reduction /withdrawal

Side effects slowly disappear as tissue levels fall. Following drug withdrawal, residual tissue-bound amiodarone may protect a patient for up to 1 month. However, the likelihood of the occurrence of arrhythmia during this period should be considered.

Paediatric population

Amiodarone is not currently indicated in children and no clinical studies in paediatric populations have been undertaken. Use in this patient population is contra-indicated (see Section 4.3, 'Contra-indications'). In published uncontrolled studies, the effective doses for children were determined as:

• Loading dose: 10 to 20mg/kg/day for 7 to 10 days (or 500mg/m^2/day if expressed per square metre)

• Maintenance dose: the minimum effective dosage should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250mg/m^2/day if expressed per square metre).

Elderly

As with all patients it is important that the minimum effective dosage 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. Particular attention should be paid it to monitoring thyroid function. (See Sections 4.3, 4.4 and 4.8, 'Contra-indications', 'Special Warnings and Precautions for Use' and 'Undesirable Effects').

Method of administration

Oral.

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 be used only in conjunction with a pacemaker.

Where there is evidence or history of thyroid dysfunction. A thyroid function test should be performed prior to therapy in all patients.

Known hypersensitivity to iodine or to amiodarone (one 200mg tablet contains approximately 75mg of iodine) or to any of the excipients (see Section 6.1, 'List of Excipients').

The combination of amiodarone with drugs which may prolong the QT interval and thereby induce Torsades de Pointes ventricular tachycardia is contra-indicated (see Section 4.5, 'Interaction with other medicinal products').

Amiodarone is contra-indicated in pregnancy (except in exceptional circumstances) or in nursing mothers (see Section 4.6, 'Pregnancy and Lactation').

4.4 Special warnings and precautions for use

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.

Anaesthesia: caution is advised in patients undergoing general anaesthesia, also in patients receiving high-dose oxygen therapy. Before surgery, the anaesthetist should be informed that the patient is taking amiodarone (see Sections 4.5 and 4.8, 'Interactions with other medicinal products and other forms of Interaction' and 'Undesirable Effects')

Cardiac disorders *(see section 4.8)* **:** too high a dose of amiodarone 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. If bradycardia is severe and symptomatic, the insertion of a pacemaker should be considered due to the long half-life of amiodarone.

Amiodarone is not contra-indicated 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 may be used with other appropriate therapies.

In patients taking amiodarone, QT interval lengthening has been seen, corresponding to prolonged repolarisation with the possible development of U-waves and deformed T waves. These changes are evidence of its pharmacological action and do not reflect toxicity.
In the elderly, heart rate may decrease markedly.
Treatment should be discontinued in the case of onset of second or third-degree AV block, sino-atrial block, or bifascicular block. Before starting amiodarone, it is recommended that an ECG be performed and serum potassium levels be assessed. Monitoring of ECG is recommended throughout treatment.
Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias has been observed with sometimes a fatal outcome. It is important, but difficult, to determine if this effect is due to a lack of efficacy of a drug from a proarrhythmic 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 (see Sections 4.5 and 4.8).
Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity
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, coadministratin 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 DAAs. 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.

Hepato-biliary disorders (*see section 4.8*): amiodarone may be associated with a variety of hepatic effects, including cirrhosis, hepatitis, jaundice and hepatic failure. In some cases, particularly following long-term therapy, the outcome of these effects has been fatal, although rarely they have occurred soon after starting treatment particularly after amiodarone intravenous. It is advisable to monitor liver function particularly transaminases before treatment and 6-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.
There have been no literature reports on the potentiation of hepatic adverse effects of alcohol; however, patients should be advised to moderate their alcohol intake while taking amiodarone.

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, opthamological examination recommended annually.

Respiratory, thoracic and mediastinal disorders (*see section 4.8*): patients should be carefully evaluated clinically and consideration given to chest X-rays before starting therapy. Of particular concern with

patients taking amiodarone is pulmonary toxicity, the symptoms of which include dyspnoea (which may be severe and unexplained by the current cardiac status), non-productive cough, and deterioration of 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. Pulmonary toxicity may also present as pulmonary fibrosis, pleuritis or pneumonitis, including hypersensitivity, alveolar, interstitial, or bronchiolitis obliterans organising pneumonitis. During treatment, if pulmonary toxicity is suspected, chest X-rays 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. However, some patients can deteriorate despite discontinuing amiodarone.

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 monitoring (including ultrasensitive TSH [usTSH]) should be performed prior to therapy in all patients. Monitoring should be carried out during treatment, at 6-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 test (free-T_3, free-T_4, usTSH) remain interpretable. Amiodarone inhibits peripheral conversion of levothyroxine (T_4) to triiodothyronine (T_3) and may cause isolated biochemical changes (increase in serum free-T_4, free-T_3 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. T3and 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 a decrease in serum usTSH level, an elevated T3and a reduced TSH response to thyrotropin releasing hormone. Elevation of reverse T3 (rT3) may also be found.
In the case of hyperthyroidism, therapy 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."

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; such recoveries may sometimes, however, be incomplete.

Skin and subcutaneous tissue disorders (*see section 4.8*)**:** hypersensitivity to sunlight may occur, which may persist after several months of discontinuation of amiodarone and patients taking amiodarone should be instructed to avoid exposure to sun or if unavoidable to use adequate protection. In most cases

symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen.

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.
ZADARON 200 mg tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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, fluoroquinolones and any drugs which prolong the QT interval.
Amiodarone raises the plasma concentrations of oral anticoagulants and phenytoin, and any other highly protein-bound drugs, through inhibition of CYP 2C9. The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. Phenytoin dosage should be reduced if signs of overdosage appear, and plasma levels may be measured.
In patients already receiving digoxin, the subsequent administration of amiodarone will increase their plasma digoxin concentration levels, resulting in signs and symptoms associated with high levels of digoxin. Clinical, ECG and biological monitoring and a reduction of digoxin dosage by half are recommended. A synergistic effect on heart rate and atrioventricular conduction is also possible.
Pharmacodynamic interactions
• Drugs inducing *Torsade de Pointes* or prolonging QT
- *Drugs inducing Torsade de Pointes*
Combined therapy with any drug known to prolong the QT interval is contra-indicated (see Section 4.3) due to the increased risk of Torsades de Pointes. They include the following:
• 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, amisulpride 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.
Concomitant use of amiodarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated). There have been rare reports of QTc interval prolongation, with or without torsades de pointes, in patients taking amiodarone with fluoroquinolones (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 certain calcium channel inhibitors (diltiazem, verapamil): potentiation of negative chronotropic properties and conduction showing 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 cause hypokalaemia and/or hypomagnesaemia: diuretics, systemic corticosteriods, tetracosactide, intravenous amphotericin.
In the case of Hypokalaemia, corrective action should be taken and QT interval monitored.
In the case of Torsades de Points, anti-arrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.
• General anaesthesia:
Caution is advised, also in patients undergoing general anaesthesia, or receiving high dose oxygen therapy. The anaesthetist should be informed that the patient is taking Amiodarone.
Potentially severe complications have been reported in patients taking Amiodarone undergoing general anaesthesia, such as bradycardia unresponsive to atropine, hypotension, disturbances of conduction, decreased cardiac output.
A few cases of adult respiratory distress syndrome, sometimes fatal, most often in the period immediately after surgery, have been observed. A possible interaction with the high oxygen concentration may be implicated.
Effect of amiodarone on other medicinal products
Amiodarone and/or its metabolites, 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 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.
• *CYP 2C9 substrates*
Amiodarone raises the plasma concentrations of oral anticoagulants (warfarin) and phenytoin by inhibition of CYP 2C9:
- *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 concentrations, 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 (e.g. rhabdomyolysis) is increased by concomitant administration of amiodarone with statins metabolised by CYP 3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended to use a statin not metabolised by CYP 3A4 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.
Effect of other 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 CYP 3A4 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 of this bradycardia effect is unknown.
Is coadministration cannot be avoided, cardiac monitoring is recommended (*see section 4.4*).

4.6 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 the pharmacological properties of the drug on the foetus and its effects on the foetal thyroid gland, its administration in pregnancy should be avoided 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 re-occurrence of life-threatening arrhythmias should be weighed against the possible hazard for the foetus.
Lactation
Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contra-indicated.

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 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%) and very rare (< 0.01%).
Due to possible serious adverse reactions affecting the lung, liver, thyroid gland, skin and peripheral nervous system, patients on long-term amiodarone treatment should be carefully supervised. These reactions can also be delayed.

Blood and lymphatic system disorders:
• Very rare:
- haemolytic anemia
- aplastic anaemia
- thrombocytopenia.
In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.
Cardiac disorders:
• Common: bradycardia, generally moderate and dose-related.
• Uncommon:
- 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: Torsade de pointes (see section 4.4 and 4.5)
Endocrine disorders (*see section 4.4*):
• Common:
- hypothyroidism
- hyperthyroidism, sometimes fatal
• Very rare

- syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Eye disorders:
• Very common: corneal microdeposits usually limited to the area under the pupil, which are usually only discernable by slit-lamp examinations. They may be associated with colored 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 progress to blindness (*see section 4.4*).
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
• Unknown: Pancreatitis/ acute pancreatitis
General disorders:
• Not known: granuloma, including bone marrow granuloma
Hepato-biliary disorders: (*see section 4.4*).
• Very common: isolated increase in serum transaminases, which is usually moderate (1.5 to 3 times 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.
Immune system disorders:
• Unknown: Anaphylactic shock/anaphylactoid reaction including shock; Angioneurotic oedema (Quincke's Oedema)
Investigations:
• Very rare: increase in blood creatinine.
Musculoskeletal and connective tissue disorders:
• Not known: lupus like syndrome
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:
- cerebellar ataxia, for which regression usually occurs after reduction of dose or withdrawal
- benign intracranial hypertension (pseudo- tumor cerebri)
- headache
- vertigo.
• Unknown: Parkinsonism, parosmia
Reproductive system and breast disorders:
• Very rare:
- epididymo-orchitis
- impotence.
Respiratory, thoracic and mediastinal disorders:
• Common: pulmonary toxicity [hypersensitivity pneumonitis, alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia (BOOP)], sometimes fatal (*see section 4.4*).
• Very rare:
- bronchospasm in patients with severe respiratory failure and especially in asthmatic patients
- surgery (possible interaction with a high oxygen concentration) (*see sections 4.4 and 4.5*).
Pulmonary haemorrhage (there have been some reports of pulmonary haemorrhage, although exact frequencies are not known)
Skin and subcutaneous tissue disorders:
• Very common: photosensitivity (*see section 4.4*).

• Common:
- eczema
- slate grey or bluish pigmentations of light-exposed skin, particularly the face, in case of prolonged treatment with high daily dosages; such pigmentations slowly disappear following treatment discontinuation.
• Very rare:
- erythema during the course of radiotherapy
- skin rashes, usually non- specific
- exfoliative dermatitis
- alopecia.
• Unknown:
- Urticaria
- severe skin reaction as toxic epidermal necrolysis (TEN), Stevens- Johnson syndrome (SJS)
- bullous dermatitis, Drug reaction with eosinophilia and systematic symptoms (DRESS).

Vascular disorders:
• Very rare: vasculitis

Metabolic and nutrition disorders:
• Unknown: Decreased appetite

Psychiatric disorders:
• Unknown: confusional state/ Delirium

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.

4.9 Overdose

Little information is available regarding acute overdosage with oral 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 an 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, beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of amiodarone (long half-life), adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended. Neither amiodarone nor its metabolites are dialyzable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group:Antiarrhythmics- ATC code -C01BD01.
ZADARON is an antiarrhythmic.
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/m²/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 a 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 has an average plasma half-life of 50 days. However there may be considered inter-patient 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 initial doses of amiodarone, for example 600mg/day, should be given 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 new distribution equilibrium to be achieved between dose adjustments.
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 notes 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 P-gp 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 P-gp substrates.

5.3 Preclinical safety data

In a 2-year 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 monohydrate,

• microcrystalline cellulose,

• corn starch,

• povidone,

• crospovidone

• magnesium stearate,

• purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Box of 60 (3 x 20) tablets, (uniform, round, slightly biconvex tablets, white) of 200 mg amiodarone in the form of amiodarone hydrochloride, in blister packs.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder
ZADA Pharmaceuticals Ltd.
Donji Bistarac without number
75 300 Lukavac
Bosnia and Herzegovina

8. Marketing authorisation number(s)
ZADARON 200 mg tablets:04-07.3-2-5196/15

9. Date of first authorisation/renewal of the authorization
ZADARON 200 mg tablets:08.11.2016.

10. Date of revision of the text
03/07/2018