UKPAR AMIODARONE HYDROCHLORIDE 100MG TABLETS
AMIODARONE HYDROCHLORIDE 200MG TABLETS
PL 12762/0190-1

UKPAR

TABLE OF CONTENTS

Lay Summary ........................................ Page 2
Scientific discussion ............................. Page 3
Steps taken for assessment .................. Page 12
Steps taken after authorisation – summary
Summary of Product Characteristics ......... Page 13
Product Information Leaflet ................. Page 33
Labelling ............................................. Page 35
AMIODARONE HYDROCHLORIDE 100MG TABLETS
AMIODARONE HYDROCHLORIDE 200MG TABLETS
PL 12762/0190-1

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Goldshield Pharmaceuticals Limited Marketing Authorisations for the medicinal products Amiodarone Hydrochloride 100mg and 200mg Tablets (PL 12762/0190-1) on 08 December 2011. These are prescription-only medicines (POM) used to control severe rhythm disorders of the heart or irregular heart beats of a sudden nature when other treatments cannot be used.

Amiodarone Hydrochloride 100mg and 200mg Tablets contain the active ingredient, amiodarone hydrochloride, which belongs to a group of medicines called anti-arrhythmics, which are used to control irregular heart rhythms.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amiodarone Hydrochloride 100mg and 200mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4

Pharmaceutical assessment Page 5

Non-clinical assessment Page 8

Clinical assessment Page 9

Overall conclusions and risk assessment Page 11
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Goldshield Pharmaceuticals Limited Marketing Authorisations for the medicinal products Amiodarone Hydrochloride 100mg and 200mg Tablets (PL 12762/0190-1) on 08 December 2011. The products are prescription-only medicines (POM) indicated only for the treatment of severe 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.

These applications were submitted under Article 10.1(a)(iii) first paragraph of Directive 2001/83/EC claiming to be generic medicinal products of Cordarone X 100mg and 200mg Tablets (Sanofi-Synthelabo, UK, now trading as Sanofi-Aventis), which were first granted a Marketing Authorisation in the UK on 29 August 1980.

Amiodarone is a class III anti-arrhythmic agent. Its principle effect on cardiac tissue is to delay repolarisation by prolonging the action potential duration (APD) and effective refractory period (ERP).

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support these applications, comparing the test product Amiodarone Hydrochloride 200mg Tablets (Goldshield Pharmaceuticals Limited, UK) versus the reference product Cordarone X 200mg tablets (Sanofi-Synthelabo, UK) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Amiodarone Hydrochloride 100mg and 200mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Amiodarone hydrochloride
Chemical Name: 2-Butyl[benzofuran-3-yl][4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride
Molecular Formula: C₂₅H₂₉I₂NO₃,HCl
Structure

Molecular weight: 682 g/mol
Appearance: A white or almost white fine crystalline powder, very slightly soluble in water, freely soluble in methylene chloride, soluble in methanol and sparingly soluble in ethanol (96%).

Amiodarone hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance amiodarone hydrochloride, except for the proposed packaging specifications and stability data, are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients maize starch, lactose monohydrate, povidone (K90), magnesium stearate, colloidal anhydrous silica, pregelatinised starch and purified water. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product Cordarone X 100mg and 200mg Tablets (Sanofi-Synthelabo, UK).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution profiles have been provided for these products and their respective reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

The Marketing Authorisation holder has committed to performing process validation on future full-scale (commercial) batches.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packaged in polyvinylchloride/aluminium blisters. These are packed into cardboard cartons with patient information leaflets in a pack size of 28 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with food.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months, with the storage conditions ‘Do not store above 30°C. Store in the original package.’

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.
Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of amiodarone hydrochloride are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of amiodarone hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics
In support of these applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, two-period, two-way crossover study to compare the pharmacokinetics of the test product Amiodarone Hydrochloride 200mg Tablets (Goldshield Pharmaceuticals Limited, UK) versus the reference product Cordarone X 200mg Tablets (Sanofi-Synthelabo, UK) in healthy adult male subjects under fasting conditions.

The subjects were given a single dose of two 200 mg tablets of the test or reference product after at least a 10 hour overnight fast. Blood samples were collected before and up to 648 hours (27 days) after each administration. The washout period between the treatment arms was between 69-82 days. The pharmacokinetic results are presented below.

| Pharmacokinetic parameters (arithmetic mean±SD, ratios and confidence intervals [CI]) of amiodarone |
|-----------------------------------------------|----------------------|-----------------------|-----------------|
| Amiodarone HCl 200mg (Test) | Cordarone X 200mg (Reference) | Test/Ref Ratio (%) | 90% CI          |
| AUC₀₋₄ (ng h/ml) | 8259±3473 | 8140±2429 | 97.6 | 89.7-106 |
| Cₘₐₓ (ng/ml) | 249±123 | 245±94.2 | 97.4 | 85.3-111 |

SD=standard deviation
AUC₀₋₄ area under the plasma concentration-time curve from time zero to t hours
Cₘₐₓ maximum plasma concentration
Ratios and 90% CI calculated from ln-transformed data

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80% to 125% for Cₘₐₓ and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC₀₋₄ and Cₘₐₓ lie within the acceptable limits. Thus, the data support the claim that the test product Amiodarone Hydrochloride 200mg Tablets (Goldshield Pharmaceuticals Limited, UK) is bioequivalent to the reference product Cordarone X 200mg Tablets (Sanofi-Synthelabo, UK).

As the 100mg and 200mg strengths of the product meet all the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), for (bio) waiver, the results and conclusions from the bioequivalence study with the 200mg tablet strength can be extrapolated to the 100mg tablet strength.
EFFICACY
The efficacy of amiodarone hydrochloride is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these generic products.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The quality characteristics of Amiodarone Hydrochloride 100mg and 200mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of amiodarone hydrochloride are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 200mg strength tablet and the reference product Cordarone X 200mg Tablets (Sanofi-Synthelabo, UK). As the 100mg and 200mg strengths of the product meet all the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), for (bio) waiver, the results and conclusions from the bioequivalence study with the 200mg tablet strength can be extrapolated to the 100mg tablet strength.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of amiodarone hydrochloride is well-known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amiodarone hydrochloride is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
AMIODARONE HYDROCHLORIDE 100MG TABLETS
AMIODARONE HYDROCHLORIDE 200MG TABLETS
PL 12762/0190-1

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 06 October 2004.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 15 October 2004.


5 The applications were granted on 13 December 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amiodarone Hydrochloride 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Amiodarone Hydrochloride 100mg.

For full list of excipient, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
Round, white, flat tablet, embossed “100” on one face and a break line on the reverse.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment should be initiated and normally monitored only under hospital or specialist supervision. Oral Amiodarone is indicated only for the treatment of severe 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.

4.2 Posology and method of administration
It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well being. The following dosage regimen is generally effective.

Initial Stabilisation
Treatment should be started with 200mg, three 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 dosage required to maintain control of the arrhythmia. The maintenance dose 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
Too high a dose during maintenance therapy can cause 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 arrhythmia during this period should be considered.

Paediatric population
The safety and efficacy of amiodarone in children has not been established. Currently available data are described in sections 5.1 and 5.2

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 this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function. (see sections 4.3, 4.4 and 4.8).

Amiodarone Hydrochloride 200mg Tablets are for oral administration.

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.

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

Known hypersensitivity to iodine or to amiodarone, or to any of the excipients. (One 200mg tablet contains approximately 37.5mg iodine).

The combination of Amiodarone Hydrochloride Tablets with drugs like moxifloxacin which may induce torsades de pointes is contra-indicated (see section 4.5).

Pregnancy - except in exceptional circumstances (see section 4.6)

Lactation (see section 4.6).

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.

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 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.
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 2nd or 3rd degree A-V block, sino-atrial block, or bifascicular block.

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 proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of drug interactions and/or electrolytic disorders (see sections 4.5. and 4.8).

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.

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 a 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, 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. 1mg/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.

Hepato-biliary 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 after Amiodarone intravenous. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter.

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 Hydrochloride 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 Hydrochloride Tablets.
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 can become unduly sensitive to sunlight, which may persist after several months of discontinuation of Amiodarone Hydrochloride Tablets. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen.

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.

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

Administration of Amiodarone Hydrochloride 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.

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

Fluoroquinolones
There have been rare reports of QTc interval prolongation, with or without torsades de pointes, in patients taking amiodarone with fluoroquinolones. Concomitant use of amidarone with fluoroquinolones should be avoided (concomitant use with moxifloxacin is contra-indicated, see above).

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 slowing effects may occur.
• 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 antiarrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.

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, most often in the period immediately after surgery, have been observed. A possible interaction with a high oxygen concentration may be implicated.

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

Drugs metabolised by cytochrome P450 3A4
When 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:
- Cyclosporin: plasma levels of cyclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of cyclosporin may be necessary to maintain the plasma concentration within the therapeutic range.
- Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are the statins, lidocaine, tacrolimus, sildenafil, fentanyl, midazolam and ergotamine.
- Simvastatin in combination with Amiodarone has been associated with reports of myopathy /rhabdomyolysis (refer to manufacturer’s prescribing information for simvastatin).

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.

Interaction with substrates of other CYP 450 isoenzymes
In vitro studies show that amiodarone also has the potential to inhibit CYP 1A2, CYP 2C19 and CYP 2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP 1A2, CYP 2C19 and CYP 2D6.

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 reoccurrence 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%), very rare (< 0.01%), not known (cannot be estimated from available data).

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.

Endocrine disorders (see section 4.4):
- Common:
  - hypothyroidism
  - hyperthyroidism, sometimes fatal.
- Very Rare:
  - syndrome of inappropriate hormone secretion (CSIADH)

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.

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
- Angioedema (there have been some reports of angioedema, although exact frequencies are not known)
Investigations:
• Very rare: increase in blood creatinine.

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.

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: 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.

• Not known: urticaria

Vascular disorders:
• Very rare: vasculitis.

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 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, 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
Amiodarone hydrochloride 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 the plasma half life is usually of the order of 50 days. However there may be considerable 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 doses of Amiodarone Hydrochloride Tablets, 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 Hydrochloride Tablets.

No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Maize Starch
Lactose Monohydrate
Povidone (K90)
Magnesium Stearate
Colloidal anhydrous silica
Pregelatinised starch
Purified water

6.2 Incompatibilities
Not applicable
6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 30ºC.
Store in the original package.

6.5 Nature and contents of container
PVC/aluminum foil blister packs containing 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Goldshield Pharmaceuticals Ltd.,
NLA Tower,
12-16 Addiscombe Road,
Croydon,
Surrey CRO OXT,
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 12762/0190

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/12/2011

10 DATE OF REVISION OF THE TEXT
08/12/2011
1 NAME OF THE MEDICINAL PRODUCT
Amiodarone Hydrochloride 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Amiodarone Hydrochloride 200mg.

For full list of excipient, see section 6.1

3 PHARMACEUTICAL FORM
Tablet

Round, white, flat tablet, embossed “200” on one face and a break line on the reverse.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment should be initiated and normally monitored only under hospital or specialist supervision. Oral Amiodarone is indicated only for the treatment of severe 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.

4.2 Posology and method of administration
It is particularly important that the minimum effective dose be used. In all cases the patient's management must be judged on the individual response and well being. The following dosage regimen is generally effective.

Initial Stabilisation
Treatment should be started with 200mg, three 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 dosage required to maintain control of the arrhythmia. The maintenance dose 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
Too high a dose during maintenance therapy can cause 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 arrhythmia during this period should be considered.

Paediatric population
The safety and efficacy of amiodarone in children has not been established. Currently available data are described in sections 5.1 and 5.2

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 this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function. (see sections 4.3, 4.4 and 4.8).

Amiodarone Hydrochloride 200mg Tablets are for oral administration.

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.

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

Known hypersensitivity to iodine or to amiodarone, or to any of the excipients. (One 200mg tablet contains approximately 37.5mg iodine).

The combination of Amiodarone Hydrochloride Tablets with drugs like moxifloxacin which may induce torsades de pointes is contra-indicated (see section 4.5).

Pregnancy - except in exceptional circumstances (see section 4.6)

Lactation (see section 4.6).

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.

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 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.
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 2nd or 3rd degree A-V block, sino-atrial block, or bifascicular block.

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 proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of drug interactions and/or electrolytic disorders (see sections 4.5. and 4.8).

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.

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-T₁ 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 a 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, 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. 1mg/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.

Hepato-biliary 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 after Amiodarone intravenous. It is advisable to monitor liver function particularly transaminases before treatment and six monthly thereafter.

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 Hydrochloride 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 Hydrochloride Tablets.
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 can become unduly sensitive to sunlight, which may persist after several months of discontinuation of Amiodarone Hydrochloride Tablets. In most cases symptoms are limited to tingling, burning and erythema of sun-exposed skin but severe phototoxic reactions with blistering may be seen.

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.

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

Administration of Amiodarone Hydrochloride 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.

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, bretylum
• 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

Fluoroquinolones
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 contra-indicated, see above).

Combined therapy with the following drugs is not recommended:
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 slowing effects may occur.
• 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 antiarrhythmic agents should not be given; pacing may be instituted and IV magnesium may be used.

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, most often in the period immediately after surgery, have been observed. A possible interaction with a high oxygen concentration may be implicated.

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

**Drugs metabolised by cytochrome P450 3A4**

When 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:

- Cyclosporin: plasma levels of cyclosporin may increase as much as 2-fold when used in combination. A reduction in the dose of cyclosporin may be necessary to maintain the plasma concentration within the therapeutic range.
- Other drugs metabolised by cytochrome P450 3A4: examples of such drugs are the statins (lipid lowering agents), lidocaine, tacrolimus, sildenafil, fentanyl, midazolam and ergotamine.
- Simvastatin in combination with Amiodarone has been associated with reports of myopathy /rhabdomyolysis (refer to manufacturer’s prescribing information for simvastatin).

**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.

**Interaction with substrates of other CYP 450 isoenzymes**

In vitro studies show that amiodarone also has the potential to inhibit CYP 1A2, CYP 2C19 and CYP 2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP 1A2, CYP 2C19 and CYP 2D6.

### 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 contra-indicated 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 reoccurrence 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 (\(\geq 10\%\)), common (\(\geq 1\%\) and < 10%); uncommon (\(\geq 0.1\%\) and < 1%); rare (\(\geq 0.01\%\) and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from available data).

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.

Endocrine disorders (see section 4.4):
- Common:
  - hypothyroidism
  - hyperthyroidism, sometimes fatal.
- Very Rare
  - syndrome of inappropriate hormone secretion (CSIADH)

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.

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
- Angioedema (there have been some reports of angioedema, although exact frequencies are not known)
Investigations:
• Very rare: increase in blood creatinine.

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.

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: 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.

• Not known: urticaria

Vascular disorders:
• Very rare: vasculitis.

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 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, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended. Neither amiodarone nor its metabolites are dialysable.

### Pharmacological Properties

#### 5.1 Pharmacodynamic properties

Amiodarone hydrochloride 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 the plasma half life is usually of the order of 50 days. However there may be considerable 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 doses of Amiodarone Hydrochloride Tablets, 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 Hydrochloride Tablets.

No controlled paediatric studies have been undertaken. In the limited published data available in paediatric patients, there were no differences noted compared to adults.

#### 5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

### Pharmaceutical particulars

#### 6.1 List of excipients

Maize Starch  
Lactose Monohydrate  
Povidone(K90)  
Magnesium Stearate  
Colloidal anhydrous silica  
Pregelatinised starch  
Purified water
6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
36 months

6.4 **Special precautions for storage**
Do not store above 30°C.
Store in the original package.

6.5 **Nature and contents of container**
PVC/aluminum foil blister packs containing 28 tablets.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Goldshield Pharmaceuticals Ltd.,
NLA Tower,
12-16 Addiscombe Road,
Croydon,
Surrey CRO OXT,
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 12762/0191

9 **DATE OF FIRST AUTHOURISATION/RENEWAL OF THE AUTHORISATION**
08/12/2011

10 **DATE OF REVISION OF THE TEXT**
08/12/2011
5. HOW TO STORE AMIODARONE TABLETS

Keep out of reach and sight of children.

Expiration date (abbreviation for expiry date).

Do not take this medicine after the expiry date shown on the pack. The expiry date refers to the last day of that month.

Do not store above 30°C. Store in the original package.

Mistakes should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Amiodarone tablet contains:

Each tablet contains the active ingredient Amiodarone hydrochloride. The tablets are available in two strengths containing 100mg and 200mg amiodarone.

Each Amiodarone Hydrochloride Tablet also contains: lactose monohydrate, microcrystalline, starch, povidone K90, colloidal anhydrous silica, pregelatinised starch and magnesium stearate (E471).

What Amiodarone tablet looks like and contents of the pack:

Amiodarone hydrochloride 100mg Tablets are round, white, flat with a central division line on one face and embossed '100' on the reverse.

Amiodarone hydrochloride 200mg Tablets are round, white, flat with a central division line on one face and embossed '200' on the reverse.

Amiodarone hydrochloride 100mg and 200mg Tablets are supplied in cartons of 28 tablets.

Marketing Authorisation Holder and Manufacturer:

Goldshield Pharmaceuticals Ltd.,
NLA Tower, 12-16 Addisonbrooke Road, Croydon, Surrey. CR0 0XT

Tel No: 02066481931

E-mail: medicalinformation@goldshielddplc.com

Manufacturer: Ayshampharm SA

Address: 6282 Morris, Switzerland

This leaflet was revised in September 2011
UKPAR Amiodarone Hydrochloride 100mg and 200mg Tablets

PL 12762/0190-1

Dosage: Adults & the elderly
• The usual dose of amiodarome is 200mg three times a day for the first week, followed by 200mg twice a day for the next week and then 200mg daily
• In some patients this may be reduced to 100mg a day
• Elderly patients may be prescribed lower doses.
Your doctor will have decided the correct dose for you. Keep taking your medicine until your doctor tells you to stop.

Children and adolescents
The safety and efficacy of amiodarone in children has not been established.
Do not stop taking it because you feel better. If you stop the tablets your condition may get worse.
If you take more Amiodarone tablets than you should
As with all medicines an overdose could be dangerous. If you, or someone else, has taken an overdose tell your doctor or go to your nearest hospital casualty department IMMEDIATELY. If you go to the doctor/hospital remember to take the leaflet and any remaining Amiodarone tablets with you so the doctor knows what you have taken.
If you forget to take Amiodarone tablet
If you forget a dose take it as soon as you remember providing it is within 2 hours. If not, wait until your next dose is due and continue as normal. Do not take two doses at once.
Do not take a double dose to make up for a forgotten dose.
If you have any further question on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amiodarone Hydrochloride Tablets can cause side effects, although not everybody gets them.

Stop taking amiodarone immediately and call your doctor if you experience signs of allergic reaction.
Signs of an allergic reaction include a rash, swelling or breathing problems, swelling of your lips, face, throat or tongue.

Amiodarone may cause side effects listed as below:
• Very common side effects (could affect more than 10 in 100 people)
  • difficulties with your vision
  • nausea (feeling sick) which subsides on dose reduction
  • feeling run down which subsides on dose reduction
  • a metallic taste which subsides on dose reduction
  • increase in the amount of hair on the face.
  • Amiodarone can cause some patients to become sensitive to the sun. You should avoid exposure of your skin to direct sunlight or sunlight. If you are sensitive then the may persist for some time after treatment stops. You should take sensible precautions when you are in the sun such as wearing a wide brimmed hat and keeping arms and legs covered. Use a total sun block cream for exposed areas of skin.

• Common side effects (could affect more than 1 in 100 people)
  • a slow pulse
  • problems with your thyroid gland (you may notice extreme restlessness and/or loss of weight, extreme tiredness and/or gain of a lot of weight)
  • disorders of the liver with jaundice including liver failure
  • a shawl which improves on dose reduction or drug withdrawal
  • nightmares, disturbed sleep patterns
  • disorders of the lungs, increased risk of infection
  • slate grey or blister discoloration of the skin exposed to light, particularly the face which disappears following treatment discontinuation.

• Uncommon side effects (could affect less than 1 in 100 people)
  • worsening of irregular heart beats sometimes leading to heart failure or other diseases of the heart
  • pins and needles, weakness of hands or legs, cramps which subsides on drug withdrawal
  • muscle pain and weakness which subsides on drug withdrawal

• Very rare side effects (could affect less than 1 in 10,000 people)
  • pallor of the skin
  • problems with the blood (you may notice bruising or nose bleeds)

3. HOW TO TAKE AMIODARONE TABLETS

Take your Amiodarone hydrochloride tablets as prescribed by your doctor and as stated on the pharmacy label on the carton of your medicine.
Swallow the tablets whole and take with a glass of water. Amiodarone Tablets can be taken with or without food.
If you are not sure how to take your tablets or how many to take, please speak to your pharmacist or doctor.

Continued Over
Amiodarone hydrochloride 100mg Tablets

Each tablet contains 100mg of Amiodarone hydrochloride.
For oral use. Take as directed by your doctor.
Important: Please read the enclosed patient information leaflet before taking this medicine.
Do not store above 30°C. Store in the original package.
Keep out of the reach and sight of children.