Safety Update CDS 12-21: Aligned with master product CORDARONE X 200
Date submitted 12.01.2021
To be implemented: 12.04.2021

Proposed professional information (clean copy)

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

ARYCOR® 100 (Tablets)

ARYCOR® 200 (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

ARYCOR 100 tablets each contain amiodarone hydrochloride 100 mg.

Contains sugar (lactose): 48,0 mg per tablet.

Contains organic iodine: Approximately 37,5 mg per tablet.

ARYCOR 200 tablets each contain amiodarone hydrochloride 200 mg.

Contains sugar (lactose): 96,0 mg per tablet.

Contains organic iodine: Approximately 75 mg per tablet.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Tablets

ARYCOR 100: White to off-white, scored, round, biconvex tablet, marked with the action potential and 100, approximately 8,0 mm in diameter.

ARYCOR 200: White to off-white, scored, round, biconvex tablet, marked with the action potential symbol and 200, approximately 10,5 mm in diameter.

4 CLINICAL PARTICULARS:

Nadia Le Hanie *RA Manager*	

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4.1 Therapeutic indications:

Prevention of tachydysrhythmias associated with Wolff-Parkinson-White-syndrome and other types of tachydysrhythmias of paroxysmal nature including supraventricular, nodal and ventricular tachycardias, atrial flutter and atrial fibrillation and ventricular fibrillation. ARYCOR should only be used when other less toxic medicines cannot be used.

4.2 Posology and method of administration:

Posology:

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.

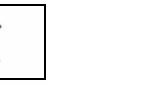
Initial stabilisation:

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

Maintenance:

After the initial period the dosage should be reduced to 200 mg daily, or less if appropriate. Rarely, the patient may require a higher maintenance dose.

The scored 100 mg tablet should be used to titrate the minimum dosage required to maintain control of the dysrhythmia. The maintenance dose should be regularly reviewed, especially where this exceeds 200 mg daily.

Nadia Le Hanie *RA Manager*	

Changeover from intravenous to oral therapy:

Oral therapy should be initiated concomitantly at the usual loading dose i.e.: 200 mg three times a day, as soon as possible after an adequate response has been obtained using ARYCOR intravenous, which should then be phased out gradually.

General considerations:

The high initial dose is necessary because of the slow onset of action whilst the necessary tissue levels of amiodarone are achieved. ARYCOR has a low acute toxicity and in this initial treatment period serious problems have not been reported. However, excessive dosage during maintenance therapy can cause side effects, which are believed to be related to excessive tissue retention of amiodarone and/or its metabolites. Side effects slowly disappear as the tissue levels fall after the dosage is reduced or ARYCOR treatment withdrawn.

If ARYCOR treatment is withdrawn, residual tissue-bound amiodarone may protect the patient for up to one month, but the likelihood of recurrence of cardiac dysrhythmias during this period should be a consideration. The important factor is that the patient requires monitoring regularly to ensure that clinical features of excessive dosage are detected and the dosage adjusted accordingly.
It is particularly important that the minimum effective dose be used, and that the patient is monitored regularly to detect the clinical features of excess amiodarone dosage. Therapy may then be adjusted accordingly.

Use in the elderly:

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 of thyroid function (see section 4.3 and 4.8)

4.3 Contraindications:

ARYCOR is contraindicated in:

- Known hypersensitivity to amiodarone or to iodine (one tablet of ARYCOR 200 contains approximately 75 mg iodine) or to any of the excipients of ARYCOR
- Sinus bradycardia and sinoatrial heart block. In patients with sick sinus syndrome (risk of sinus arrest), severe atrioventricular conduction disorders (high grade AV block, bifascicular or trifascicular block) or sinus node disease, unless a pacemaker is fitted
- Thyroid dysfunction (see section 4.4)
- Pregnancy (see section 4.6
- Lactation (see section 4.6)
- Combined therapy with medicines which may induce Torsade de Pointes (see section 4.5).

Paediatric Patients: The safety and efficacy of ARYCOR in paediatric patients have not been established. Therefore, its use in paediatric patients is not recommended.

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4.4 Special warnings and precautions for use:

ARYCOR is intended for use only in patients with the indicated life-threatening dysrhythmias because its use is accompanied by substantial toxicity.

ARYCOR has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10-17 % in some series of patients with ventricular dysrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of some patients. Pulmonary toxicity has been fatal about 10 % of the time.

Liver injury is common with ARYCOR, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. **ARYCOR can exacerbate the dysrhythmias e.g. by making the dysrhythmias less well-tolerated or more difficult to reverse. This has occurred in 2-5 % of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5 %.** Due to the long elimination half-life of ARYCOR**,** the risk of prodysrhythmic effects is prolonged after amiodarone is stopped.

Even in patients at high risk of dysrhythmic death, in whom the toxicity of ARYCOR is an acceptable risk, ARYCOR poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilise alternative medicines first.

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The difficulty of using ARYCOR effectively and safely itself poses a significant risk to patients.

Patients with the indicated dysrhythmias must be hospitalised while the loading dose of ARYCOR is given, a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment.

Please refer to detailed discussion under each point below.

ARYCOR may induce photosensitisation in some patients. Patients being treated with ARYCOR should be instructed to avoid exposure to sunlight and to use total sunblock barrier creams and other protective measures during therapy.

ARYCOR should be avoided in patients with porphyria as it may precipitate an attack.

Due to the very long elimination half-life of ARYCOR, adverse events may disappear only several months after discontinuation of ARYCOR. As undesirable effects are usually dose-related, the minimum effective maintenance dose should be given.

Monitoring:

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

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Further, as ARYCOR may induce hypothyroidism or hyperthyroidism, particularly in patients with personal history of thyroid disorders, clinical and biological (usTSH) monitoring is recommended before starting ARYCOR. This monitoring should be carried out during treatment and for several months following its discontinuation. Serum usTSH level should be measured when thyroid dysfunction is suspected.

In particular in the context of chronic administration of antidysrhythmic medicines, cases of increase in the ventricular defibrillation and/or pacing threshold of the pacemaker or implantable cardioverter defibrillator device have been reported, potentially reducing its efficacy. Therefore, a repeated verification of the functioning of the device before and during ARYCOR treatment is recommended.

Thyroid function:

ARYCOR can induce erratic results from thyroid function tests (see section 4.8).

Thyroid hormone abnormalities:

Both hyper- and hypothyroidism have occurred during, or soon after, treatment with ARYCOR. Simple monitoring of the usual biochemical tests is confusing because some (PBI and ^{131}I uptake) are invalidated and others (T4, T3 and FTI) may be altered where the patient is clearly euthyroid. Clinical monitoring is therefore recommended and should be continued for some months after discontinuation of ARYCOR treatment. This is particularly important in the elderly. In patients whose history indicates an increased risk of thyroid dysfunction, regular testing is recommended.

Hyperthyroidism:

Clinical features of hyperthyroidism such as [~~mass~~] weight loss, [1] asthenia, restlessness, increase in heart rate or a recurrence of the cardiac dysrhythmia, angina or congestive heart failure, should alert the clinician. The diagnosis may be supported by the finding of an elevated serum tri-iodothyronine (T_3), a low level of thyroid stimulating hormone (TSH as measured by high sensitivity methods) and a reduced TSH response to thyrotrophin releasing hormone (TRH). Elevation of reverse T3(rT3) may also be found.

In the case of hyperthyroidism, ARYCOR therapy should be withdrawn. The diagnosis is supported by a clear decrease in serum ultrasensitive TSH (usTSH) level, in which case, ARYCOR should be withdrawn.

Courses of anti-thyroid medication have been used for the treatment of severe thyroid hyperactivity; large doses may be required initially. These may not always be effective and concomitant high dose corticosteroid therapy may be required for several weeks. Recovery may occur after a few months following withdrawal of treatment. Clinical recovery precedes the normalisation of thyroid function tests. Severe cases, with clinical presentation of thyrotoxicosis, and sometimes fatal, require emergency therapeutical management (see section 4.8).

Hypothyroidism:

The clinical features of hypothyroidism such as [~~mass~~] weight[1] gain, cold intolerance and reduced activity or excessive bradycardia should alert the clinician. The onset may be abrupt. The diagnosis may be supported by the presence of an elevated serum TSH level and an exaggerated TSH response to TRH. The thyroxine (T4), T3 and free thyroxine index (FTI) may be low.

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Thyroid hypofunction usually resolves within 3 months of cessation of therapy; it may be treated cautiously with L-thyroxine. In life-threatening situations, ARYCOR therapy can be continued, in combination with L-Thyroxine. The dose of L-Thyroxine is adjusted according to TSH levels.

Eye disorders:

During long-term administration regular ophthalmological examination is recommended. If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. Appearance of optic neuropathy and/or optic neuritis requires ARYCOR withdrawal due to the potential progression to blindness.

Cardiac disorders:

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

Although ARYCOR is not contraindicated in patients with latent or manifest heart failure, caution should be exercised as existing heart failure may be worsened by ARYCOR. In this case, ARYCOR should be associated with the usual cardiotonic and diuretic treatment.

The pharmacological action of amiodarone induces ECG changes such as QT prolongation (related to prolonged repolarisation) with the possible development of U-waves. However, these changes do not reflect toxicity.

In the elderly, heart rate may decrease markedly.

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Treatment should be discontinued in case of onset of 2nd or 3rd degree A-V block, sinoatrial block or bifascicular block.

Cases of severe, potentially life-threatening bradycardia and heart block have been observed when ARYCOR is used in combination with sofosbuvir alone or in combination with another hepatitis C virus (HCV) direct acting antiviral (DAA), such as daclatasvir, simeprevir, or ledipasvir. Therefore, coadministration of these medicines with ARYCOR is not recommended (see section 4.5).

If concomitant use with ARYCOR cannot be avoided, it is recommended that patients are closely monitored when initiating sofosbuvir alone or in combination with other DAAs. Patients who are identified as being at high risk of bradydysrhythmia should be continuously monitored for at least 48 hours in an appropriate clinical setting after initiation of the concomitant treatment with sofosbuvir.

Due to the long half-life of amiodarone, appropriate monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on sofosbuvir alone or in combination with other direct DAAs.

Patients receiving these hepatitis C medicines with ARYCOR, 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.

Onsets of new dysrhythmias or worsening of treated dysrhythmias, sometimes fatal, have been reported. It is important, but difficult, to differentiate a lack of efficacy of the medicine from a prodysrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. The prodysrhythmic effect of ARYCOR has usually occurred in the context of QT prolonging factors such as medicine interactions and/or electrolyte disorders. Despite QT interval prolongation, ARYCOR exhibits low torsadogenic activity. (see sections 4.5 and 4.8)

In a retrospective survey of 192 patients with ventricular tachydysrhythmias, 84 required dosage reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15–20 % overall frequencies of discontinuation due to adverse reactions.

The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dosage adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalisation. Attempts to substitute other anti~~ar~~rhythmic medicines when ARYCOR must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when ARYCOR is not effective: it still poses the risk of interaction with whatever subsequent treatment is tried.

Primary graft dysfunction (PGD) post cardiac transplant:

In retrospective studies, ARYCOR use in the transplant recipient prior to heart transplant has been associated with an increased risk of PGD.

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

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

Pulmonary disorders:

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

Cases of severe respiratory complications, sometimes fatal, have been observed usually in the period immediately following surgery (adult acute respiratory distress syndrome); a possible interaction with a high oxygen concentration may be implicated (see sections 4.5).

Hepatic disorders:

Close monitoring of liver function tests (transaminases) is recommended as soon as ARYCOR is started and regularly during treatment. Acute liver disorders (including severe hepatocellular insufficiency or hepatic failure, sometimes fatal) and chronic liver disorders may occur with oral

and intravenous forms and within the first 24 hours of IV ARYCOR. Therefore, the ARYCOR dose should be reduced or the treatment discontinued if the transaminases increase exceeds three times the normal range.

Clinical and biological signs of chronic liver disorders due to oral ARYCOR may be minimal (hepatomegaly, transaminases increased up to 5 times the normal range) and reversible after treatment withdrawal, however fatal cases have been reported.

Neuromuscular disorders:

ARYCOR may induce peripheral sensorimotor neuropathy and/or myopathy. Recovery usually occurs within several months after ARYCOR withdrawal, but may be incomplete.

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 ARYCOR treatment should be discontinued immediately.

Concomitant use with other medicines:

Concomitant use of ARYCOR is not recommended with the following medicines: beta-blockers, heart rate lowering calcium channel inhibitors (verapamil, diltiazem), stimulating laxative agents which may cause hypokalaemia (see section 4.3 and 4.5).

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Anaesthesia:

Before surgery, the anaesthetist should be informed that the patient is taking ARYCOR (see section 4.5)

Lactose Intolerance:

Since ARYCOR tablets contain lactose (monohydrate), patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption e.g. galactosaemia, should not take ARYCOR.

4.5 Interactions with other medicines and other forms of interaction:

PHARMACODYNAMIC INTERACTIONS:

Medicines inducing Torsade de Pointes or prolonging QT:

- **Medicines inducing Torsades de Pointes*, which may be fatal*:**

  The risk of Torsade de pointes may be increased when ARYCOR is used in combination with other medicines which directly or indirectly prolong the QT interval

- **Combined therapy with medicines that may induce Torsade de Pointes is contraindicated** (see section 4.3)
  - Antidysrhythmic[~~s~~] medicines such as Class Ia, sotalol, bepridil, disopyramide, quinidine.
  - Non-antidysrhythmic medicines such as vincamine, some neuroleptic medicines, cisapride, erythromycin IV, pentamidine (when administered parenterally)
  - Concomitant administration with dysrhythmogenic medicines for example phenothiazine antipsychotics
  - Certain antihistamines such as mizolastine
  - Antimalarials such as quinine, mefloquine, chloroquine, halofantrine

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- Lithium and tricyclic antidepressants such as doxepin, maprotiline, amitriptyline.

- **Medicines prolonging QT:**

  Co-administration of ARYCOR with medicines known to prolong the QT interval 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. Fluoroquinolines should be avoided in patients receiving ARYCOR (e.g. moxifloxacin, ciprofloxacin).

Medicines lowering heart rate or causing automaticity or conduction disorders:

Combined therapy with the following medicines is not recommended:

Beta-blockers and heart rate lowering calcium channel inhibitors (verapamil, diltiazem) as automaticity (excessive bradycardia) and conduction disorders may occur.

Medicines which may induce hypokalaemia:

Combined therapy with the following medicines is not recommended:

Stimulating laxative medicines which may cause hypokalaemia such as senna and bisacodyl thus increasing the risk of Torsade de Pointes; other types of laxatives should be used.

Caution should be exercised when using the following medicines in combination with ARYCOR:

- Diuretics inducing hypokalaemia, either alone or combined
- Systemic corticosteroids (gluco-, mineralo-), adrenocorticotrophic hormone (ACTH)
- Amphotericin B (IV)

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

General anaesthesia (see section 4.4)**:**

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

Cases of severe respiratory complications (adult acute respiratory distress syndrome), sometimes fatal, have been observed usually in the period immediately following surgery. A possible interaction with a high oxygen concentration may be implicated.

EFFECT OF ARYCOR ON OTHER MEDICINAL PRODUCTS:

Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.
Due to the long half-life of amiodarone, interactions may be observed for several months after discontinuation of ARYCOR.

- **PgP substrates:** Amiodarone is a P-gp inhibitor. Co-administration with P-gp substrates is expected to result in an increase of their exposure.
  - **Digoxin*:*** The plasma concentrations of digoxin may be raised with the concomitant administration of ARYCOR. Administration of ARYCOR to a patient already receiving digoxin may bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Monitoring of ECG and

plasma levels is recommended and digoxin dosage should be adjusted accordingly. A synergistic effect on heart rate and atrioventricular conduction is also possible.

- ***Dabigatran*:** Caution should be exercised when ARYCOR is co-administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran as per its package insert.

- **CYP2C9 substrates:** Amiodarone raises the concentrations of CYP2C9 substrates such as warfarin or phenytoin by inhibition of the cytochrome P450 2C9.
  - ***Warfarin:*** The effects of warfarin and other oral anticoagulants may be enhanced by concomitant administration of ARYCOR. ARYCOR raises the concentration of warfarin by inhibition of the cytochrome P450 2C9. The combination of warfarin with ARYCOR may exacerbate the effect of the warfarin thus increasing the risk of bleeding. It is necessary to monitor prothrombin (INR) levels more regularly and to adjust oral doses of warfarin both during treatment with ARYCOR and after discontinuation of ARYCOR treatment
  - **Phenytoin:** Consideration should be given to the possibility that ARYCOR may alter the plasma concentrations of other medicines, particularly those which are highly protein-bound e.g. phenytoin. The combination of phenytoin and ARYCOR may lead to phenytoin overdosage, resulting in neurological signs. Clinical monitoring should be undertaken and phenytoin dosage should be reduced if overdosage signs appear; phenytoin plasma levels may be determined when necessary. In addition, plasma ARYCOR concentrations may be decreased by phenytoin.
- **CYP2D6 substrates:**
  - **Flecainide:** ARYCOR raises plasma concentrations of flecainide by inhibition of the cytochrome CYP2D6. Therefore, flecainide dosage should be adjusted accordingly and the patient closely monitored.

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- **CYP P450 3A4 substrates:** When such medicines are co-administered with amiodarone, an inhibitor of CYP3A4, this may result in a higher level of their plasma concentrations, which may lead to a possible increase in their toxicity:
  - **Ciclosporin**: its combination with ARYCOR may increase cyclosporin plasma levels. Dosage should be adjusted
  - **Fentanyl**: its combination with ARYCOR may enhance the pharmacologic effects of fentanyl and increase the risk of its toxicity
  - **Statins**: the risk of muscular toxicity (e.g rhabdomyolysis) is increased by concomitant administration of ARYCOR with statins especially those metabolised by CYP3A4 such as simvastatin, atorvastatin and lovastatin. It is recommended not to use a statin combined with ARYCOR
  - **Other medicines metabolised by CYP3A4**: lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihydroergotamine, ergotamine, colchicine.
- **Others:**

  The effects of clonazepam may be enhanced by concomitant administration of ARYCOR, and plasma concentrations of procainamide, and quinidine may be raised.

EFFECT OF OTHER PRODUCTS ON ARYCOR:

CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit ARYCOR metabolism and to increase its exposure. It is recommended to avoid CYP3A4 inhibitors (e.g. grapefruit juice and certain medicines during treatment with ARYCOR.

Plasma ARYCOR concentrations may be increased by cimetidine and other inhibitors of metabolising enzymes CYP3A4 including HIV-protease inhibitors.

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Coadministration of ARYCOR with sofosbuvir alone or in combination with another HCV direct acting antiviral (such as daclatasvir, simeprevir, or ledipasvir) is not recommended as it may lead to serious symptomatic bradycardia. The mechanism for this bradycardia effect is unknown. If coadministration cannot be avoided, cardiac monitoring is recommended (see section 4.4).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

In view of amiodarone's effect on the foetal thyroid gland, ARYCOR is contraindicated during pregnancy.

Breastfeeding:

ARYCOR is excreted into the breastmilk in significant quantities and breastfeeding is contraindicated (see section 4.3).

4.7 Effects on the ability to drive and use machines:

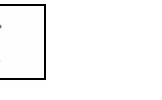
Driving or operating machinery should be carried out with caution because ARYCOR causes blurred vision and coloured halos in dazzling light.

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 %), unknown (cannot be estimated from available data).

Blood and lymphatic system disorders:

Very rare: haemolytic anaemia, aplastic anaemia and thrombocytopenia

Nadia Le Hanie *RA Manager*	

Endocrine disorders:

Common: hypothyroidism and hyperthyroidism, sometimes fatal

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

Nervous system disorders:

Common: tremor, nightmares and sleeplessness.

Uncommon: peripheral neuropathy and/or myopathy, usually reversible on withdrawal of the medicine.

Very rare: ataxia, benign intracranial hypertension, fatigue, vertigo and headache.

Eye disorders:

Very common: corneal micro-deposits usually limited to the area under the pupil. They may be associated with coloured halos in dazzling light or blurred vision. Corneal micro-deposits consist of complex lipid deposits and are reversible following discontinuation of treatment.

Very rare: optic neuropathy/neuritis that may progress to blindness. Papilloedema, corneal degeneration, photosensitivity, eye discomfort, scotoma, lens opacities and macular degeneration have also been reported.

Cardiac disorders:

Common: bradycardia, generally moderate and dose-related. ECG changes, i.e. QT interval lengthening corresponding to prolonged repolarisation; U-waves and deformed T-waves may occur.

Uncommon: onset of new dysrhythmia or worsening of existing dysrhythmia, sometimes followed by cardiac arrest. Conduction disturbances (sinoatrial block, AV block of various degrees).

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

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Vascular disorders:

Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders:

Common: pulmonary toxicity (alveolar/interstitial pneumonitis or fibrosis, pleuritis, bronchiolitis obliterans organising pneumonia/BOOP), sometimes fatal

Very rare: bronchospasm in patients with severe respiratory failure and especially in asthmatic patients. Adult acute respiratory distress syndrome, sometimes fatal, usually immediately after surgery (possible interaction with a high oxygen concentration)

Gastrointestinal disorders:

Very common: nausea, vomiting, metallic taste, usually occurring with loading dosage and resolving with dose reduction

Hepato-biliary disorders:

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 cholestasis with jaundice including hepatic failure, which are sometimes fatal

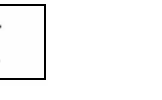
Very rare: chronic liver disease (pseudo alcoholic hepatitis, cirrhosis), sometimes fatal

Skin and subcutaneous tissue disorders:

Very common: photosensitivity.

Common: slate grey or bluish pigmentations of the skin 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

Nadia Le Hanie *RA Manager*	

Reproductive system and breast disorders:

Very rare: epididymo-orchitis and impotence.

Investigations:

Very rare: Increased serum creatinine

Post-marketing data:

Blood and lymphatic system disorders: neutropenia, agranulocytosis

Immune system disorders: angioedema (Quincke's Oedema), anaphylactic/anaphylactoid reaction including shock

Metabolism and nutrition disorders: decreased appetite

Psychiatric disorders: confusional state/delirium, hallucination

Nervous system disorders: Parkinsonism, parosmia

Cardiac disorders: Torsade de Pointes (see section 4.4 and 4.5)

Gastrointestinal disorders: pancreatitis/ acute pancreatitis, dry mouth, constipation

Respiratory, thoracic and mediastinal disorders:

pulmonary haemorrhage

Skin and subcutaneous tissue disorders: urticaria, eczema, severe skin reactions sometimes fatal including Toxic Epidermal Necrolysis (TEN)/Stevens- Johnson syndrome (SJS), bullous dermatitis, Drug reaction with Eosinophilia and Systematic Symptoms (DRESS)[1] (see section 4.4)

Musculoskeletal and connective tissue disorders:

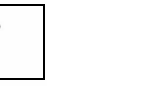
lupus like syndrome

Reproductive system and breast disorders: libido decreased

General disorders and administration site conditions:

granuloma, including bone marrow granuloma

Injury, poisoning and procedural complications:

Nadia Le Hanie *RA Manager*	

primary graft dysfunction post cardiac transplant (section 4.4)

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: Email: za.drugsafety@sanofi.com or Tel: 011 256-3700, or

SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in the elderly patients or during digoxin therapy. In these circumstances, ARYCOR treatment should be withdrawn.

In the event of an overdosage general supportive measures should be employed. The patient should be monitored and if bradycardia ensues beta-adrenostimulants or glucagon may be given. Spontaneously resolving attacks of ventricular tachycardia may also occur. Due to the pharmacokinetics of ARYCOR, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

5. PHARMACOLOGICAL PROPERTIES:

A 6.2 Cardiac depressants.

Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class III. ATC code: C01BD01.

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5.1 Pharmacodynamic properties:

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

5.2 Pharmacokinetic properties:

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.

The terminal elimination half-life is about 50 days with a range of about 20 to 100 days due to its extensive tissue distribution. On stopping prolonged amiodarone therapy, a pharmacological effect is evident for a month or more.

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

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 creatinine (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-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour induction. In the mouse, carcinomas were not observed, but a dose-dependent thyroid follicular hyperplasia was seen.

These effects on the thyroid in rats and mice are most likely due to effects of amiodarone on the synthesis and/or release of thyroid gland hormones. The relevance of these findings is considered to be low.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Maize starch

povidone

colloidal silicon dioxide

magnesium stearate

lactose monohydrate (see section 2)

6.2 Incompatibilities:

Not applicable.

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6.3 Shelf life:

36 months

6.4 Special precautions for storage

The tablets should be protected from light, and stored at or below room temperature (25 ºC). Keep the tablets in the blister until required for use.

6.5 Nature and contents of container:

ARYCOR 100:

White to off-white, scored tablets containing 100 mg of amiodarone hydrochloride in a blister pack.

Packs of 30 tablets

ARYCOR 200:

White to off-white, scored tablets containing 200 mg of amiodarone hydrochloride in a blister pack.

Packs of 30 tablets.

7 HOLDER OF CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd.

2 Bond Street

Midrand, 1685

South Africa

8 REGISTRATION NUMBER[~~S~~]:

ARYCOR 100: 32/6.2/0513

ARYCOR 200: 32/6.2/0514

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Proposed professional information (clean copy)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

ARYCOR 100: 18 February 2000

ARYCOR 200: 14 May 2001

10 DATE OF REVISION OF THE TEXT:

To be allocated

NAMIBIA:

Scheduling status: NS2

Reg. No.:

ARYCOR 100 tablets: 05/6.2/0344

ARYCOR 200 tablets: 05/6.2/0345

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