New Zealand Datasheet

1 Lodi 50 mg/mL concentrate for infusion

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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amiodarone hydrochloride 150 mg/3 mL

3 PHARMACEUTICAL FORM

Lodi Concentrate for Infusion is a clear, colourless or slightly yellow solution for administration intravenously. It is available in glass ampoules containing 150 mg of amiodarone hydrochloride in 3 mL.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment must only be administrated under specialist or hospital supervision.

Tachyarrhythmias associated with Wolff-Parkinson-White Syndrome. All types of tachyarrhythmias including; nodal and ventricular tachycardias, supraventricular, atrial flutter, ventricular fibrillation and fibrillation when other medications are unable to be used.

Lodi Concentrate for Infusion is to be used when a rapid response is necessary.

4.2 Dose and method of administration

SPECIAL REQUIREMENTS FOR ADMINISTRATION ARE REQUIRED FOR THIS PRODUCT. SEE 'INSTRUCTIONS FOR USE AND HANDLING' PRIOR TO ADMINISTRATION.

Lodi Concentrate for Infusion must be administered only when the facilities are available for cardiac defibrillation and monitoring in the chance they are required. Intravenous infusion is the preferred administration route as intravenous injection is associated with hemodynamic risks (circulatory collapse and severe hypotension) and is normally not advised.

The daily dose of Lodi Concentrate for Infusion depends on the seriousness of the illness. The dosage and the time of the treatment should be decided by the doctor.

The regular recommended dosage is 5 mg for every kilogram of body weight administered by intravenous infusion over a period of 20 minutes to 2 hours. This should be diluted to 250 mL with 5% glucose solution.

LODI CONCENTRATE FOR INFUSION IS INCOMPATIBLE WITH SALINE SOLUTION AND MAY ONLY BE ADMINISTERED IN A 5% GLUCOSE INTRAVENOUS INFUSION SOLUTION.

The administration may be repeated 2 to 3 times per day. The maximum dosage per day is 1,200 mg (about 15 mg per kilogram of body weight) in up to 500 mL of 5% glucose solution over 24 hours. Based on clinical response the rate of infusion should be adjusted.

In a life-threatening clinical emergency, Lodi Concentrate for Infusion may be administered as a slow injection of 150 mg to 300 mg in 10-20 mL 5% glucose over a time of 3 minutes' minimum. This should be completed on the basis of the clinician's judgement. This procedure must not be repeated for at least fifteen minutes. A patient who requires this

procedure, must be carefully monitored i.e. in an intensive care ward.

Lodi Concentrate for infusion must not be mixed with other formulations in the same infusion solution or syringe.

Preparations that contain less than two 3 mL ampoules of Lodi Concentrate for Infusion in 500 mL 5% glucose are considered unstable and must not be used.

When Lodi Concentrate for Infusion is administered by infusion it may decrease drop size and, if appropriate, changes should be made to the infusion rate.

Recurrent or constant infusion via the peripheral veins may result in local inflammation and discomfort. When recurrent or constant infusion is expected, it is recommended for the administration to be completed by a central venous catheter.

Amiodarone can be absorbed into PVC infusion bags and administration sets probably because of the existence of plasticisers in plastic PVC. Therefore, it is vital that the preparation of Lodi Concentrate for Infusion solution is completed immediately before use in either glass or PVC rigid bottles without plasticisers.

Medical equipment or devices that contain plasticisers, for example, DEHP (di-2-ethylhexyl phthalate) in the presence of amiodarone solution may cause filtering out of DEHP. Therefore, to minimise the exposure of DEHP to the patient, the last amiodarone dilution for infusion may rather be administered through non-DEHP enclosing sets.

Use in the Elderly
As with all patients it is vital that the minimum effective dosage is used. Carefully calculate how much Lodi Concentrate for Infusion the patient should receive and monitor the patient's heart rate and thyroid function closely. Patients in this group may be more susceptible to conduction defects and bradycardia if too great a dose is used.

Instructions for use and handling
Reports of crystallisation have been received for Lodi Concentrate for Infusion.

Inspect each Lodi ampoule and check for crystalline content prior to administration.

The use of both filter needles and in-line filters is a requirement for the administration of Lodi Concentrate for Infusion.

Before use, the solution concentrate should be visually inspected for clarity, particulate matter, discolouration and the integrity of the ampoule. The solution concentrate should only be used if it is clear, free from particles and the ampoule is undamaged and intact.

With all ampoules on opening there is the remote possibility that glass particles may enter the solution. With Lodi Concentrate for Infusion, a filter needle is a requirement when drawing up the concentrate for infusion from the ampoule and then the filter needle should be replaced with a new needle when administering into a solution for infusion.

The dilution is to be made under aseptic conditions.

The solution should only be used if it is clear, free from particles and the container is undamaged and intact.

It is a requirement that the diluted solution should be administered to the patient through an in-line filter.

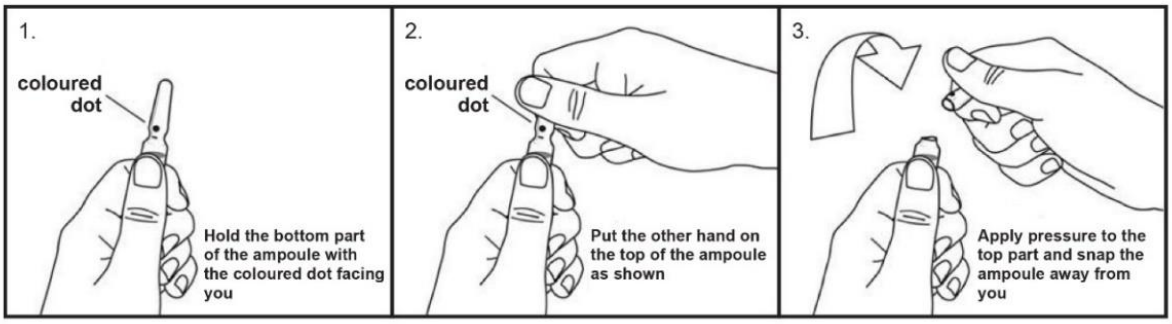
Do not use this medicine if you notice the packaging or ampoule is damaged.

Lodi Concentrate for Infusion is intended for single dose only.

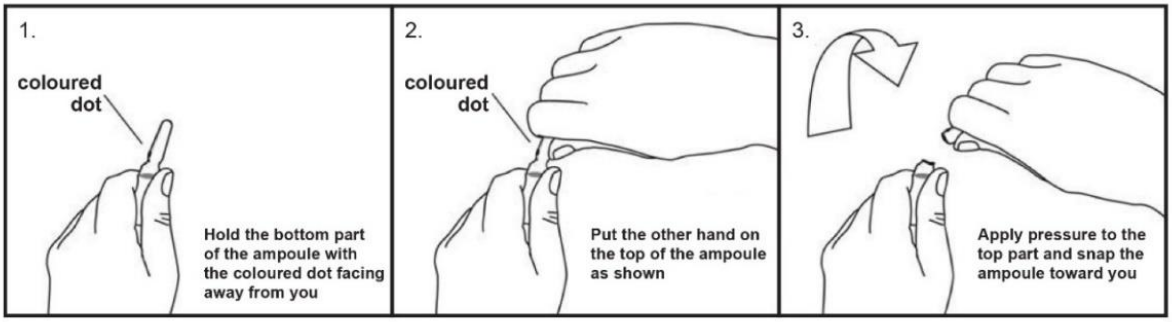
Any unused solution should be discarded immediately after initial use.

Use an antiseptic to clean the ampoule before opening.

A. Snap back method



B. Snap forward method



The Concentrate for Infusion in the ampoule should be diluted with glucose 5%.

For each ampoule, a maximum of 250 mL of glucose 5% infusion should be used. Greater dilutions are unstable. Lodi Concentrate for Infusion, diluted in 5% glucose solution to a concentration of <0.6 mg/mL, is not stable. Solutions containing less than two Lodi Concentrate for Infusion ampoules in 500 mL of 5% glucose are unstable and must not be used.

The diluted Lodi solution is physically and chemically stable for 12 hours at room temperature. However, from a microbiological viewpoint, the product should be use immediately after dilution.

4.3 Contraindications

Identified hypersensitivity to amiodarone or iodine or to any of the excipients.

Pregnancy and Lactation (Please refer to Use in Pregnancy and Use in Lactation).

Lodi Concentrate for Infusion should only be used in combination with a pacemaker in patients with sick sinus syndrome (risk of sinus arrest), in patients where bradycardia or AV block may cause syncope or patients with severe atrioventricular conduction disorders.

Sino-atrial heart block and sinus bradycardia.

Lodi Concentrate for Infusion is contraindicated in patients with a history of thyroid dysfunction or there is evidence of a thyroid dysfunction.

Combined treatment with medications that may induce torsades de pointes (Please refer to Interactions).

Lodi Concentrate for Infusion is contraindicated in patients who experience hypotension, cardiomyopathy, severe respiratory failure, severe arterial hypotension, heart failure and circulatory collapse. It is also contraindicated in bi- or tri-fascicular conduction disorders, except if a functioning permanent pacemaker is fitted or, if the patient is residing in a special care unit and amiodarone is administered under the cover of electrosystolic pacing.

Due to the benzyl alcohol content, Lodi Concentrate for Infusion is contraindicated in babies less than one month old or premature neonates as it can cause reactions that are considered toxic and allergic (Please refer to Warnings and Precautions – Paediatric Use).

4.4 Special warnings and precautions for use

Before the initiation of treatment, it is recommended to complete a serum potassium measurement and an ECG.

Proceed with caution in cases of uncompensated or severe heart failure, hypotension or severe respiratory failure.

Due to haemodynamic risks of circulatory collapse and severe hypotension, intravenous injection is generally not advised; it is preferable to use intravenous infusion where possible. In emergency situations where other therapies have been unsuccessful, intravenous injection can be administered only under constant monitoring in an intensive care unit (ECG, blood pressure). To avoid possible irreversible collapse, intravenous injection must not be administered again within fifteen minutes after the initial injection even if the initial administration was only one ampoule. Lodi IV should be administered via a central venous line, when possible to prevent a reaction at the injection site (Please refer to Dosage and Administration). No other preparations should be mixed in the same syringe. No other preparations should be injected into the same IV line. If Lodi Concentrate for Infusion is to be continued, this must be through IV transfusion.

Thyroid Hormone Abnormalities

It is known that amiodarone may stimulate thyroid disorders (Please refer to Adverse Effects). This is more prevalent in patients with a family history or personal history of thyroid disorders. Because of this, clinical and biological observation (ultrasensitive TSH (usTSH) assay) is advised prior to the start of treatment, throughout treatment and for numerous months after treatment has been discontinued. If thyroid dysfunction is presumed, serum usTSH levels must be assessed. Severe instances where there is a clinical appearance of thyrotoxicosis (in some instances fatal), will require emergency treatment management.

Iodine is present in amiodarone and therefore may intervene with the radio-iodine uptake. However, thyroid function analyses stay interpretable (free-T3, free-T4, usTSH). Amiodarone reduces the peripheral conversion of thyroxine (T4) to triiodothyronine (T3). This might result in rare biochemical variations (for example, an increase in serum free-T4 or a slight decrease of free-T3 or even normal variations) in patients that are clinically euthyroid. In these cases, there is no reason to withdraw amiodarone therapy.

If subsequent side effects occur, hypothyroidism should be suspected: reduced activity, weight gain, excessive bradycardia and cold intolerance (these side effects may be minor). The identification of hypothyroidism is reinforced by a distinct increase in serum usTSH. Following one to three months of treatment discontinuation, euthyroidism is generally

obtained. Amiodarone treatment can be sustained in life threatening circumstances, when in combination with L-Thyroxine. Based on TSH levels, the dosage of L-Thyroxine is modified.

Hyperthyroidism
During treatment with Lodi Concentrate for Infusion or following numerous months after treatment, hyperthyroidism may occur. Side effects that may present and should warn the physician include angina, weight loss, congestive heart failure and the onset of arrhythmia. The identification of hyperthyroidism is reinforced by a distinct reduction of serum ultrasensitive TSH (usTSH) level. If this occurs, Lodi Concentrate for Infusion should be withdrawn from treatment. After the withdrawal of treatment, recovery typically happens within several months. Clinical recovery leads the stabilisation of thyroid function tests. Emergency therapeutic management is required in severe (sometimes fatal) cases, with a clinical presentation of thyrotoxicosis. Amiodarone dosage should be modified in all individual cases (beta-blockers, anti-thyroid drugs and corticosteroid therapy).

Neuromuscular Disorders
Amiodarone might stimulate peripheral sensorimotor neuropathy and/or myopathy. After amiodarone withdrawal, recovery typically occurs within a few months, and in some instances, may be incomplete.

Pacemakers/Implantable Defibrillators
In circumstances of antiarrhythmic medication being chronically administered, there have been reports of an increase in ventricular defibrillation and/or the pacing threshold of implantable cardioverter defibrillator devices or pacemakers, possibly affecting their effectiveness. Thus, confirmation of the functioning of these devices is recommended before and during amiodarone treatment.

Anaesthesia
Prior to surgery the anaesthetist must be notified that the patient is on amiodarone medication.

Cardiac Disorders
ECG changes are induced by the pharmacological action of amiodarone. This includes QT prolongation, which is in relation to extended repolarisation (with the potential occurrence of U-waves). Please note that these changes do not indicate toxicity.

Lodi Concentrate for Infusion is not contraindicated in patients experiencing latent or manifest heart failure, however, care should be taken as current heart failure might sometimes become worse. In these cases, amiodarone must be linked with the typical cardiotonic and diuretic treatment.

An unnecessary dosage may result in atropine resistant bradycardia and to conduction disturbances (especially in elderly patients or throughout digitalis therapy). Amiodarone, as well as disopyramide and quinidine, has initiated atypical ventricular tachycardia (Please refer to Adverse Effects – Cardiovascular). For patients with preceding history of atypical ventricular tachycardia, amiodarone must be avoided. The use of amiodarone at larger doses is not advised in patients with a history of atypical ventricular tachycardia formerly stimulated by an alternative antiarrhythmic medicine.

In the case of bifascicular, trifascicular block, sinoatrial block or 2nd or 3rd degree A-V block onset, treatment should be discontinued.

There have been reports of the start of different arrhythmias or the deterioration of treated arrhythmias (sometimes fatal). It is imperative, but challenging, to distinguish an absence of efficacy of the medication from a proarrhythmic effect, even if this is, or is not related with a

deterioration of the cardiac condition.

In comparison with other antiarrhythmic medications, proarrhythmic effects are seldom reported with amiodarone. Proarrhythmic effects usually occur when there are drug interactions and / or electrolytic disorders (Please refer to Interactions with other Medicines).

When amiodarone is administered in combination with sofobuvir only, or in combination with an additional hepatitis C virus (HCV) direct acting antiviral (DAA) (for example, simeprevir, davlatasvir or ledipasvir), there have been reports where severe, possibly life-threatening bradycardia and heart block have been seen. Thus, administration of amiodarone in combination with these medications is not recommended. In cases where amiodarone must be administered alongside these medications, it is advised that patients are carefully monitored when administering sofobuvir only, or in combination with others DAAs. Patients who are acknowledged as having a high risk of bradyarrhythmia must be monitored constantly for a minimum of forty-eight hours in a suitable clinical environment following administration of the combined treatment with sofosbuvir. Patients who have discontinued amiodarone treatment over the last few months but are to start administration with sofosbuvir only or in combination with other direct DAAs should be closely monitored due to the long half-life of amiodarone. Patients must be notified of the symptoms of heart block and bradycardia and should be guided to obtain urgent advice if they experience any of these symptoms especially patients taking these hepatitis C medications alongside amiodarone (with or without other medication that lowers the heart rate).

ECG Monitoring
Patients receiving amiodarone on a long-term basis should receive regular ECG monitoring. Due to amiodarone accumulating in the myocardial tissues, U waves, T waves that are deformed and QT prolongation (connected to prolonged repolarisation) may appear in the ECG. This is not a signal for withdrawing amiodarone.

The continuation of the QT interval ensues in the majority of all patients as it is associated with the antiarrhythmic and electrophysiological properties of amiodarone. Continuation of the QT exceeding 0.60 seconds rather than the widening of QTC or QRS, may be a significant warning indication that needs therapy modification. If the dosage is too high, this may result in severe bradycardia and conduction disruptions with the presence of an idioventricular rhythm (atypical ventricular tachycardia; torsades de pointes). This is observed predominantly in elderly patients or during other antiarrhythmic therapy or digitalis. Amiodarone must be withdrawn temporarily in such conditions.

Ocular Changes
In the majority of patients, corneal deposits will develop (Please refer to Adverse Effects – Ocular) and conventional ophthalmological monitoring (for example, visual acuity, slit lamp biomicroscopy and ophthalmoscopy) is suggested. If decreased or blurred vision arises, ophthalmological examination (incorporating fundoscopy) must be quickly performed. The development of optic neuritis and/or optic neuropathy will require amiodarone withdrawal due to potential blindness.

Pulmonary Disorders
Radiological and clinical confirmation of pneumonitis and/or pulmonary fibrosis have been previously reported. This has occasionally presented as unexplained or disproportionate dyspnoea (Please refer to Adverse Effects – Respiratory). Patients undertaking long term treatment, or if a diagnosis is suspected should be given regular chest X-ray's that are performed routinely. The effect has typically been able to be reversed with a decrease or withdrawal of amiodarone treatment and/or corticosteroid therapy.

The appearance of dyspnoea or a non-productive cough might be connected to pulmonary

toxicity, for example, interstitial pneumonitis (Please refer to Adverse Effects). Extremely rare incidents of interstitial pneumonitis have been observed with amiodarone administered intravenously. If a diagnosis is suspected, in patients developing isolated effort dyspnoea or in association with worsening of their general health, for example, weight loss, fatigue and fever, a chest X-Ray should be completed. Interstitial pneumonitis is usually reversible after an early withdrawal of amiodarone with clinical signs generally resolving between three to four weeks followed by a gradual radiological and lung pulmonary function recovery (within some months). Therefore, amiodarone treatment should be reconsidered. Corticosteroid therapy should also be considered.

Immediately following surgery for adult acute respiratory distress syndrome, very rare events of severe respiratory difficulties, (in some cases fatal), have been observed. A potential implication may be a result of high oxygen concentration interaction.

Hepatic Dysfunction
Consistent monitoring of liver function tests (transaminases) is suggested and recommended immediately after amiodarone is administered and throughout treatment.

Liver enzyme levels are often elevated (for example, serum alanine amionotransferase, serum aspartate aminotransferase, and glutamyl transpeptidase) and occur frequently in patients receiving treatment with amiodarone and in various circumstances are asymptomatic. The liver enzyme variations appear to be dose related rather than idiosyncratic. Careful monitoring of hepatic function (using liver function tests) is highly recommended immediately after amiodarone has been administered and throughout treatment due to cases of hepatotoxicity that have been occasionally reported (Please refer to Adverse Effects – Hepatic).

During the initial twenty-four hours of treatment with amiodarone IV, acute liver disorders (for example, hepatic failure (occasionally fatal) or severe hepatocellular insufficiency) and chronic liver disorders might occur with intravenous and oral forms. Thus, the dosage of amiodarone should be decreased or the amiodarone treatment withdrawn if the transaminases increase surpasses 3 times the normal range.

Biological and clinical signs of chronic liver disorders in relation to amiodarone taken orally, may be insignificant (hepatomegaly, transaminases amplified up to 5 times the standard range) and revocable after the withdrawal of treatment, yet fatal situations have been reported.

Use in Hepatic Disease
Amiodarone should be administered with extreme care in patients with hepatic disease, this is due to the possible risk of hepatotoxicity and/or accumulation.

Skin Reaction
Photosensitivity is relatively common (Please refer to Adverse Effects – Dermatological) and there is a wide range of skin reactions, which range from an increased inclination to suntan to extreme burning and erythema and swelling of the uncovered area. Using a high protection sunscreen, or a decrease in the current dosage for amiodarone can alleviate the intensity of these reactions. Patients should be directed to take protective actions against sun exposure and to avoid the sun when possible during treatment.
In some cases, patients have had a change in skin pigmentation of a slate grey/purple colour on exposed skin areas. This change in pigmentation may be prevented if the dosage is kept to the minimum effective dosage. If the pigmentation is cosmetically unpleasant, alternative treatment is possible and amiodarone should be withdrawn.

Amiodarone must be withdrawn from treatment without delay if symptoms appear of Toxic

Epidermal Necrolysis (TEN) (a developing skin rash frequently with mucosal lesions or blisters) or Steven-Johnson Syndrome (SJS).

Neurological Toxicity
Patients who are receiving a high dose over a long term (usually more than 400 mg per day), may experience peripheral neuropathy (Please refer to Adverse Effects – Nervous System).

Intracellular inclusion bodies (comparable to ones observed in the skin) have been exhibited in peripheral nerve fibres. Myopathy and sensorimotor neuropathy (with a glove and stocking distribution), have been observed in some patients. It has also been demonstrated, segmental demyelination of the nerve fibres histologically. After the withdrawal of amiodarone, the neurological problem is gradually and moderately resolved.

Use in Renal Disease
Amiodarone is renally excreted renally at a minimum. This implies that modifying the dosage of amiodarone in patients with renal failure is not required.

Hypotension
When amiodarone is administered via the intravenous route, hypotension may occur. In particular cases, hypotension may be unmanageable, developing into fatal outcomes (Please refer to Adverse Reactions – Amiodarone Infusion).

Drug Interactions
Concurrent usage of amiodarone with the following drugs: heart rate lowering calcium channel inhibitors (diltiazem and verapamil), beta-blockers or stimulating laxative agents are not recommended as they may cause hypokalaemia (Please refer to 'Interactions with Other Medicines'.

Paediatric Use
It is not recommended to use amiodarone in paediatric patients as the safety and efficacy as not been determined.

Lodi Concentrate for Infusion contains benzyl alcohol and should not be administered to premature neonates or neonates (ages less than one month old) as there have been known instances of "gasping syndrome" that is known to be fatal. This has been reported following other intravenous solution administration containing benzyl alcohol. Symptoms comprise of a rapid onset of gasping syndrome, bradycardia, hypotension, and cardiovascular collapse.

Use in the Elderly
Heart rate might reduce substantially in the elderly.

Carcinogenicity
Amiodarone initiated a dose associated increase in thyroid follicular tumours (carcinomas and/or adenomas) in a carcinogenicity study in rats. This was seen in both sexes of the rats. Though the mutagenicity results were negative, an epigenic instead of a genotoxic process is suggested for this kind of tumour production. For the mouse, there was no observation of carcinomas but dosage reliant thyroid follicular hyperplasia was noticed. The significance of these results to humans are not known. It has been indicated through clinical experience that amiodarone is known to affect thyroid function.

4.5 Interaction with other medicines and other forms of interactions

Combined Therapy inducing Torsades de Pointes
It is contraindicated to use medication in combined therapy that may induce 'torsade de pointes' (Please refer to Contraindications):

Antiarrhythmic Agents, for example: Class IA antiarrhythmic agents, which include:

- Quinidine: following amiodarone administration to a stable medication schedule of quinidine, the development of atypical ventricular tachycardia with QT prolongation may occur. It is believed that this is due to either a modification of the receptor or protein binding of quinidine. During concomitant amiodarone treatment, quinidine serum levels can escalate significantly. If amiodarone treatment is combined with quinidine treatment, vigilant monitoring of quinidine serum levels and electrocardiogram for QT interval prolongation is indicated.
- Disopyramide: amiodarone and disopyramide combined therapy causes a QT interval increase.
- Procainamide: amiodarone and procainamide combined therapy causes a significant increase of the serum level of procainamide and in addition may increase cardiac, gastrointestinal and neural toxicity.
- Bepridil
- Mexiletine: amiodarone and mexiletine combined therapy causes a QT interval increase.
- Sotalol

Non-antiarrhythmic agents, for example: erythromycin IV (or pentamidine IV), vincamine, cisapride and several neuroleptic agents, due to potentially lethal 'torsades de pointes' increased risk.

Drugs prolonging QT
Combined therapy of amiodarone with medication recognised to extend the QT interval should be administered on a vigilant assessment of the possible benefits and risks for individual patients due to the risk of *torsade de pointes* increasing (Please refer to Precautions). All patients must be observed for QT prolongation.

Patients taking amiodarone should not be given fluoroquinolones.

Medication that lowers the heart rate or causes conduction disorders or automaticity:

Combined therapy or amiodarone with the below medications is not recommended:
Calcium Antagonists: combined therapy of amiodarone with medication of the calcium antagonist category may result in bradycardia and conduction disorders.

Beta adrenergic blocking drugs: amiodarone should be administered with caution in patients already on beta blockers as amiodarone also displays non-competitive alpha and beta adrenergic inhibition. Amiodarone in this circumstance may instigate bradycardia and conduction disorders might ensue.

MAO Inhibitors: amiodarone combined therapy with monoamine oxidase inhibitors are contraindicated due to theoretical reasons.

Medication which may cause hypokalaemia:

Co-administration with the following medications are not recommended:
Laxative medication (stimulating): use may result in hypokalaemia and thus increases the possibility of 'torsades de pointes'. Different varieties of laxative medication should be administered.

While administering the following medication in combination with amiodarone, proceed with care for medication such as systemic corticosteroids (for example, gluco- and mineralo-) and tetracosactirn, amphotericin B through IV and diuretics that induce hypokalaemia (individually or combined).

To avoid the beginning of hypokalaemia (and to remedy hypokalaemia); it is required that the QT interval is checked and reviewed. In the situation of 'torsades de pointes', antiarrhythmic medication should not be provided (initiation of ventricular pacing; IV magnesium may be administered).

General anaesthesia (Please refer to sections 4.4 and 4.8)
In patients administered general anaesthesia alongside amiodarone, potentially severe concerns have been observed. These include, hypotension, bradycardia unresponsive to atropine, reduced cardiac output and disturbances of conduction.

Severe respiratory complications (for example, acute respiratory distress syndrome in adults) have been observed (in some cases fatal) in the time immediately following surgery. A high oxygen concentration interaction may be potentially implicated.

Effect of amiodarone on other medication
CYP 1A1, CYP 1A2, CYP 3A4, CYP 2C9, CYP 2D6 and P-glycoprotein are inhibited by amiodarone and/or its main metabolite, desethylamiodarone. This may increase exposure of their substrates.

Interactions might be noticed for a few months after amiodarone discontinuation due to the long half-life of amiodarone.

P-gp substrates
Combined therapy with P-gp substrates is anticipated to have an increase of their exposure as amiodarone is a P-gp inhibitor.

Digitalis: Administration of digoxin in combination with amiodarone to patients currently receiving digitalis, escalates the plasma digoxin concentrations by approximately 70 percent. This may be due to the reduction in digoxin clearance and thus toxicity is precipitated and could result in conduction disturbances with the arrival of idioventricular rhythm and severe bradycardia. It is unknown how this mechanism of action appears however, amiodarone may displace glycoside tissue or intervene with the excretion of digoxin. Monitoring of the ECG and digoxin plasma levels should be completed with care, and patients observed for digoxin toxicity clinical observations. Digoxin therapy dosage may need to be adjusted.

Dabigatran: When amiodarone and dabigatran are administered in combination, care should be applied due to the risk of bleeding. The dabigatran dosage may need to be adjusted as per the label.

CYP 2C9 substrates
Amiodarone increases CYP 2C9 substrate concentrations (for example, warfarin and/or phenytoin) by inhibiting the cytochrome P450 2C9.

Warfarin and additional anticoagulant agents: Amiodarone increases warfarin concentration. Warfarin and amiodarone in combination, increases the effect of the anticoagulant treatment and increases the potential of bleeding. Additional monitoring on a frequent basis of prothrombin (INR) level and adjustment of the dosage of oral anticoagulant throughout therapy with and following the discontinuation of amiodarone treatment is required.

Phenytoin: Plasma concentrations of phenytoin are amplified by amiodarone. The use of phenytoin and amiodarone in combination, can result in increases of the plasma phenytoin levels with indications of overdose (predominantly neurological indications). Clinical observation should be taken with care and the dosage of phenytoin should be decreased as soon as signs of overdose emerge; phenytoin plasma levels should be reviewed.

CYP 2D6 substrates
Flecainide: It is recommended that the dose of flecainide is adjusted when used in combination with amiodarone. This is due to increases in the flecainide concentration plasma levels by the inhibition of cytochrome CYP 2D6.

CYP 3A4 substrates
When medicines are administered alongside amiodarone (a CYP 3A4 inhibitor), this may ensue in an increased amount of their plasma concentrations, which may lead to a potential rise in their toxicity.

Statins that are metabolised by CYP 3A4: It is advised to administer a statin that is not metabolised by CYP 3A4 when provided with amiodarone. Statins that are metabolised by CYP 3A4 (for example, atorvastatin, lovastatin and simvastatin) have an increased risk of muscular toxicity when used in combination with amiodarone.

Cyclosporin: the dose should be modified.

Fentanyl: amiodarone in combination with fentanyl may increase the fentanyl pharmacologic effects and amplify the possibility of its toxicity.

Other: colchicine, dihydroergotamine, ergotamine, lignocaine, midazolam, sildenafil, tacrolimus, triazolam,

Effect of other Medication on amiodarone
Amiodarone metabolism may be inhibited and have increased exposure by CYP 3A4 inhibitors and CYP 2C8 inhibitors.

Therefore, it is recommended to not use CYP 3A4 inhibitors, for example, grapefruit juice and particular other medication while having treatment with amiodarone.

Combined therapy of amiodarone with sofosbuvir only or in combination with additional HCV direct acting antiviral, for example, simeprevir, daclatasvir or ledipasvir, is not recommended because it may result in serious symptomatic bradycardia. The method of this bradycardia effect is not known. If combined therapy is unable to be avoided, cardiac observation is required (Please refer to Precautions).

Additional deliberation should be given to the option that amiodarone may modify the plasma concentration of other medication predominantly for medicines that are highly protein bound.

Amiodarone Effects on Laboratory Tests

Thyroid Function Tests
Amiodarone has a structural similarity to the thyroxine molecule by containing two atoms of iodine. An amiodarone maintenance dosage of 300 mg has been shown to generate 9 mg per day of iodine (at steady state), which is well in surplus of the maximum standard dietary intake.

As a result of taking the medication and in the nonappearance of any clinical thyroid dysfunction, variations in laboratory tests of thyroid function may ensue, inconsistent in degree and number. Usually, the serum thyroxine (T4), PBI, free thyroxine index (FTI) iodine uptake and reverse triiodothyronine (rT3) increases and serum triiodothyronine (T3) decreases.

In about 12 percent of patients, abnormalities may happen, either multiple or single.

Specifically, a low T3 syndrome has been observed, as with other medication, for example, dexamethasone.

General
It has been observed that heparin and aminophylline have a physical incompatibility with amiodarone when combined in an infusion administration. It is suggested that Lodi Concentrate for Infusion is not administered with other medicines.

4.6 Fertility, pregnancy and lactation
Use in Pregnancy
Category C
Amiodarone is contraindicated in pregnancy. The use of amiodarone is best not to be used in the 3 months prior to pregnancy and during pregnancy. This is because of amiodarone and its major metabolite's long half-life, and the capability to cause bradycardia and abnormal thyroid function in the foetus If amiodarone exposure to the foetus is inevitable, thyroid function (incorporating TSH) should be measured straightaway in the newborn infant.

Amiodarone does traverse the placenta; however, no teratogenic effects have been detected in animals. In a woman (35 years old) in one study who was prescribed amiodarone in the final weeks of pregnancy, transplacental passage of amiodarone was 10% and desethylamiodarone was 25%. Differences in maternal thyroid function remained comparable to what was observed in other patients administered amiodarone therapy however, there was no clinical evidence of hyperthyroidism (Please refer to Adverse Effects – Endocrine). On day four, the baby's TSH level was normal and it was clinically euthyroid and had no goitre. Still, the authors warn against the usage of amiodarone in women who are pregnant or women expected to conceive while being treated with amiodarone. Amiodarone treatment should be stopped a few months before conception due to the long half-life of amiodarone. Amiodarone has potential adverse effects on the foetal thyroid which are concerning because the administration of iodine (in a dosage of amiodarone there is 75 mg in a 200 mg dose) during pregnancy might trigger foetal goitre, mental retardation and hypothyroidism.

A different patient was administered 800 mg amiodarone for 1 week with a maintenance dose of 400 mg daily while she was 34 weeks pregnant. The levels of amiodarone in the neonate were 25% of the mother's level. The infant was bradycardic through labour and for the initial 48 hours following birth, although it's thyroid and liver function tests were normal.

Lodi Concentrate for Infusion contains benzyl alcohol. Medications containing benzyl alcohol when administered to neonates or premature neonates have been linked with a "gasping syndrome" that is known to be fatal. As benzyl alcohol might traverse the placenta, Lodi Concentrate for Infusion must be administered with caution in pregnancy.

Use in Lactation
Lodi Concentrate for Infusion should not be administered to mothers who are breastfeeding. Amiodarone and its desethyl metabolite are known to be secreted in breast milk and its safety has not been established in new-borns. If a circumstance requires that amiodarone be administered to a mother who is breastfeeding, alternate infant feeding should be introduced.

4.7 Effects of ability to drive and use machines
Lodi Concentrate for Infusion is not likely to affect the ability to drive or use machinery.

4.8 Undesirable effects
It has been reported that amiodarone can instigate frequent and possible serious toxicity. The incidence, severity and variety of the effects differed from each study. The majority of

the adverse effects are in relation to the dose and period of amiodarone use, simultaneous use of additional antiarrhythmic medication, the seriousness of the original disease condition, and the specific variation in pharmacokinetic profile of the medication.

The following principle has been applied for the classification of adverse events: - Very common (> = 10%), common (≥ 1% and < 10%); uncommon (≥ 0.1% and < 1%); rare (≥ 0.01% and < 0.1%); very rare (< 0.01%) and unknown.

Cardiac Disorders:
Common: bradycardia (usually moderate), intrahisian block.
Rare: exacerbation of cardiac failure.
Very Rare: beginning or deterioration of arrhythmia, occasionally followed by cardiac arrest, marked bradycardia, sinus arrest which involves discontinuation of amiodarone (particularly in elderly patients or patients who have sinus node dysfunction, conduction disturbances (AV block of many level and sinoatrial block).
Other: Atypical Ventricular Tachycardia (torsade de pointes)

Atypical ventricular tachycardia induced by amiodarone has been described. Previous information describes other medications or clinical studies with combination therapy which may have been implicated. In two patients, administered amiodarone and disopyramide, on withdrawal of amiodarone, the disopyramide did not cause atypical ventricular tachycardia.

Arrhythmia occurrence, or deterioration of pre-existing arrhythmia, followed by cardiac arrest in a few reports has been observed. In consideration of present knowledge, it may not be possible to distinguish what may be due to an underlying cardiac condition, or the medication, or from what may be due to the underlying cardiac condition or what may be due to a lack of efficacy of treatment. These results are rarely reported in comparison with other anti-arrhythmic medications generally, and they appear in general in circumstances of particular medicine connections or electrolyte disorders.

In patients exhibiting bradycardia, atropine has been effectively used.

Dermatological:
Common: Photosensitivity.
Rare: Facial pigmentation (slate grey colour), skin discolouration (blue).
Very Rare: Sweating, alopecia, enhanced pustular psoriasis.
Unknown: Eczema, Urticaria, severe skin reactions (occasionally fatal), including bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, a medication reaction with eosinophilia, systematic symptoms. Erythema (throughout radiotherapy), facial flushing and hair loss.

Photosensitivity can be relieved usually by the use of an effective sunscreen and other protective actions. Dermatological adverse effects are partly reliant on dosage and the treatment duration.

Non-specific skin rashes (also involving incomparable reports of exfoliative dermatitis) have been reported, although this relationship has not been officially established with amiodarone.

Eye Disorders:
Very Common: Corneal microdeposits.
Very Rare: Visual acuity interference in connection with corneal microdeposits, blurred vision, gritty eyes, burning or itching.
Unknown: Optic neuropathy or optic neuritis that may develop into blindness.

In one study microdeposits were present in 30%, 55% and 95% in five to eight weeks, three

months and nine months, respectively. In a different study, corneal deposits took eight weeks to appear, but were apparent in all patients. Amiodarone keratopathy is in relation to dosage and duration of therapy. Patients on a low dosage of 100 mg per day to 200 mg per day retained clear corneas or exhibit stage 1 changes (portrayed by the conjoining of fine punctate, greyish golden brown opacities into a linear horizontal arrangement in the inferior cornea). Those on elevated dosages of 400 mg per day to 1,400 mg per day exhibited stage 2 (portrayed by extra arborizing and horizontal lines) and stage 3 (portrayed by a verticillate, whorl like pattern) variations which are determined on the period of therapy. The keratopathy develops, even with a decreased dosage, however, absolute regression follows when the medication is removed. Absolute clearing is observed to occur from between three and seven months after the removal of the amiodarone.

Corneal microdeposits are fundamentally benign initiating no visual disturbances and have merely given rise to symptoms rarely, for example, visual coloured haloes in intense light or vision that is blurred. Corneal microdeposits comprise of complex lipid deposits and are revocable ensuing the discontinuation of therapy.

Several cases of neuropathy/optic neuritis have been reported. Currently, the amiodarone relationship has not been officially established. If blurred vision or decreased vision happens, ophthalmological examination comprising fundoscopy should be appropriately performed. The appearance of optic neuropathy and/or optic neuritis demands the withdrawal of amiodarone due to the possibility of progression to blindness.

Endocrine Disorders:
Common: Abnormal thyroid function tests, weight gain.
Very rare: Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Unknown: Hyperthyroidism.

Endocrine Effects on the Thyroid
During amiodarone treatment or quickly thereafter, both hyper- and hypothyroidism have been reported. Straightforward monitoring of the standard biochemical tests are complicated due to some (PBI and ^{131}I uptake) tests becoming overturned and other tests (T4, T3 and FTI) may be distorted where the patient is obviously euthyroid. Prior to amiodarone therapy, during and for some months after, clinical monitoring is recommended. If thyroid dysfunction is assumed, serum usTSH levels should be evaluated.

Thyroid hyperactivity indications are asthenia, congestive heart failure, recurrence of cardiac dysrhythmia, onset of angina, restlessness and/or weight loss, Diagnosis can be confirmed by the result of an increase in serum triiodothyronine (T3), a low level of thyroid stimulating hormone (TSH) and a decreased TSH response to thyrotropin releasing hormone (TRH). An increase of reverse tri iodothyronine (rT3) may also be found. Hyperthyroidism appearing throughout amiodarone treatment can be serious (and can result in death) due to the concurrence of ischaemic heart disease and/or life threatening arrhythmias in the majority of patients. The risk of emerging hyperthyroidism continues for at least three months following the discontinuation of amiodarone therapy. Patients who are given amiodarone should be directed to discuss with their physician on the occasion of the recurrence of tachycardia or an exacerbation of angina following successful therapeutic response (even when episodes can occur up to six months following the discontinuation of the medication).

Hypothyroidism indications are excessive bradycardia, reduced activity and/or weight gain, in excess of the anticipated effect of amiodarone and should raise concerns for the clinician. The commencement of these side effects may be sudden. The diagnosis can be reinforced by the occurrence of a raised serum TSH level and an amplified TSH response to TRH. Thyroxine (T4), T3 and free thyroxine index (FTI) may be subtle.

Anti-thyroid medications have been administered for the treatment of thyroid hyperactivity. Considerable dosages may be initially required.

Thyroid hypofunction can be remedied carefully with L-thyroxine.

Gastrointestinal Disorders:
Very Rare: Nausea, vomiting, constipation, anorexia, dysgeusia, dry mouth, pancreatitis/acute pancreatitis, decreased appetite and angioneurotic oedema (Quincke's oedema).

General Disorders and Administration Site Conditions:
Common: Injection site reactions – cellulitis, erythema, extravasation, induration, infection, infiltration, inflammation, necrosis, oedema, pain, phlebitis, pigmentation changes and thrombophlebitis

Inflammation of the veins after intravenous infusion can potentially be avoided by the use of a central venous catheter.

Haematological:
Rare: There has been a suggestion of a hypersensitivity reaction: renal involvement with increased creatinine levels, vasculitis and thrombocytopenia.
Very Rare: haemolytic anaemia or aplastic anaemia. Chronic renal failure deteriorating (one case has been reported of symptomatic hypercalcaemia).
Unknown: There have been related findings of bone marrow granulomas in patients administered amiodarone. The significance of this in a clinical setting is unknown. Bone marrow depression has been recorded in one case, however the effect and cause of this was unknown. There have been reports of neutropenia and agranulocytosis.

Hepato-biliary disorders:
Common: Biochemical abnormalities, abnormal liver function tests (high AST, ALT and alkaline phosphatase).
Very rare: acute liver disorders with increases of serum transaminases and/or jaundice including hepatic failure (occasionally fatal). Serum transaminases isolated increase (typically moderate of 1.5 to 3 times the average range) at the start of treatment. This increase may resume back to normal levels with a decrease in the dosage or even unexpectedly.
Unknown: Chronic liver disease (cirrhosis, pseudo alcoholic hepatitis).

In cases of acute liver disorder with increased serum transaminases and/or jaundice, treatment of amiodarone should be withdrawn. In most cases this should result in normalisation of liver function tests. Although, a few cases of death in relation to acute liver disorders have uncommonly been reported.

Clinical indications and biological changes with chronic liver disease may be insignificant (likely hepatomegaly, where transaminases are elevated 1.5 to 5 times than standard). During treatment with amiodarone, regular monitoring of liver function is recommended. Once therapy has stopped, clinical and biological anomalies typically revert but fatality has been reported.

Immune System Disorders:
Very Rare: Anaphylactic/anaphylactoid reaction, shock, positive antinuclear antibodies and increased immunoglobulin levels (recorded in one patient with amiodarone stimulated pulmonary fibrosis).
Unknown: Angioedema.

Musculoskeletal and Connective Tissue Disorders:
Very Rare: Lupus like syndrome.
Unknown: Back pain.

Nervous System Disorders:
Common: abnormal nerve conduction, dizziness, fatigue, gait abnormalities, headaches, insomnia, nightmares paraesthesia, sleep disorders, tremor, vertigo, vivid dreams, extrapyramidal symptoms.
Uncommon: peripheral sensorimotor neuropathy and/or myopathy.
Very Rare: headache, benign intra-cranial hypertension (pseudo tumour cerebri), nerve conduction delay.

Extrapyramidal symptoms appeared in 4 percent of patients (2 of 51 patients) who were administered 800 mg per day of amiodarone over four to eighteen months and in one patient who was administered 100 mg per day over five to six days respectively.

Some reports of neuropathy (indicating amiodarone-induced neurolipidosis) have been observed. In 2 reports, electron microscope results are comprehensive. In one patient neuromyopathy has been reported who was given interchanging doses of 200 mg per day to 400 mg per day. In 5 patients, peripheral neuropathy has been reported who were given between 600 mg per day and 800 mg per day over a period ranging four to eighteen months. In four to six percent of patients, proximal muscle weakness has been reported, with thigh muscle being concerned in patients given high doses of 800 mg per day or more.

Psychiatric:
Common: Chronic anxiety.
Rare: Hallucinations, confusional state/delirium.

Respiratory, Mediastinal and Thoracic Disorders:
Common: Pulmonary toxicity (alveolar/interstitial pneumonitis or fibrosis, bronchiolitis obliterans organising pneumonia (BOOP), pleuritis. Note these have sometimes been recorded as fatal
Very Rare: Interstitial fibrosis or pneumonitis (sometimes fatal), severe respiratory complications for example, adult acute respiratory distress syndrome (can be fatal) and bronchospasm and/or apnoea (in the case of severe respiratory failure and particularly in patients who have asthma).
Unknown: Pulmonary fibrosis and/or alveolitis, pulmonary haemorrhage.

While amiodarone is used in treatment, patients who develop dyspnoea or any other new respiratory symptom, should have a chest X-ray. This should be completed whether the side effect is in isolation or connected with general health deterioration (for example, fatigue, fever and/or weight loss).

Early amiodarone withdrawal from treatment can usually reverse the effects of pulmonary disorders. Corticosteroid therapy might be considered also. Clinical indications typically settle over three to four weeks, followed by gradual improvement in lung function and radiological lung function over a few months.

When a diagnosis of interstitial fibrosis or pneumonitis is suspected, the patient should be given a chest X-ray. Re-evaluation of amiodarone treatment should be completed due to interstitial pneumonitis being commonly reversible after the timely removal of amiodarone. Corticosteroid treatment should be contemplated.

In the time immediately after surgery there have been very rare cases of severe respiratory complications (acute adult respiratory distress syndrome) and may result in a fatality. A

potential interaction with high oxygen concentrations may be involved.

Vascular Disorders:
Common: Hypotension (or collapse) in cases of rapid injection or overdosage, low blood pressure (usually moderate and transient).
Very Rare: Hot flushes.

Other:
There have been cases of epididymo-orchitis and additionally some reports of impotence.

Benign intracranial hypertension/pseudotumour cerebri and cerebellar ataxia are reported very rarely.

4.9 Overdose
In literature, there is a report of attempted suicide with 2,600 mg of amiodarone, where no clinical symptoms (i.e. variations in the heart rate or blood pressure were observed). The ECG uncovered significant QT interval lengthening and inversion of the T wave in the precordial leads with a temporary withdrawal of the R wave in leads V1 to V4, imitating an antero-septal infarction.

Another report of attempted suicide was reported with the use of amiodarone 8 g. In this case, the one symptom described was profuse perspiration with no reports of dyspnoea, cyanosis or reduced sensitivity. Over the observed period of three months, no clinical side effects were reported. Overdosage might result in severe bradycardia and conduction disturbances with the arrival of an idioventricular rhythm. This may occur especially in elderly patients or throughout digitalis treatment. In these situations amiodarone should be withdrawn temporarily and if required glucagon or beta adrenostimulants administered. In the incident of toxic dose ingestion, gastric lavage should be used to decrease the absorption and furthermore, general supportive measures should be used.

For the management of amiodarone overdose, contact the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class III - ATC code: C01BD01

Amiodarone has a very comprehensive range of activity due to it being a Class III antiarrhythmic agent. Amiodarone prolongs the action potential period and consequently the refractory period of atrial, ventricular and nodal tissues. A rise in the refractory period of the atrial tissue is a main action contributing to atrial tachyarrhythmias control.

A decrease in the penetrability of the A-V node, of anterograde and retrograde mutually, supports the efficacy of amiodarone in nodal tachycardias instigated by the re-entry through the A-V node.

Several mechanisms are used to explain amiodarone’s action on ventricular arrhythmias. The influence on the atrium and A-V node results in a decrease in the occurrence of stimuli accessing the ventricle. This in turn provides the ventricular cell mass time to repolarise (in circumstances where there has been refractory period desynchronisation). Additionally, an increase of the refractory period of the ventricular contractile fibres and the His-Purkinje system decreases or averts micro re-entry. With the use of amiodarone, coronary blood flow is increased, the requirements of cardiac oxygen are decreased (without the production of negative inotropic effects) and additionally suppresses ectopic pacemakers. This is

especially effective in arrhythmias linked with angina pectoris or ischaemic damage.

Amiodarone site and mode of action can be reviewed by its effect on myocardial electrophysiology.

Myocardial Electrophysiology

Sinus Node:

Amiodarone reduces sinus automaticity by decreasing the gradual diastolic depolarisation gradient within the nodal cell. This is not facilitated through the parasympathetic or sympathetic system and is a direct effect.

Atrio-Ventricular (A-V) Node:

Amiodarone decreases the pace of conduction and increases the A-V node refractory period.

His-Purkinje System:

Amiodarone increases the A-V node refractory period but does not adjust the pace of conduction of the His-Purkinje system.

Contractile Fibres:

Amiodarone increases the action ability but does not modify the amount of depolarisation of the ventricular myocardial or atrial (an effect that is more pronounced in the atria compared to the ventricles).

5.2 Pharmacokinetic properties

Overall, the pharmacokinetic data in association with amiodarone is not complete. Following administration orally, amiodarone is partly and intermittently absorbed. There is broad patient variation with absolute bioavailability ranging from 22% to 86%. A factor in establishing the obtainability of the medication may be first-pass metabolism in the wall of the gut and/or in the liver.

For estimation of the plasma levels of amiodarone, an HPLC method is available. Yet, the significance of this is restricted because the association of plasma level and therapeutic effect is yet to be established. Steady state plasma levels are normally about 1 to 2 µg per mL, however, inter-subject differences are common.

Following an especially large single dose, noticeably higher results have been reported. Peak plasma concentrations following a single dosage of 1,600 mg and a single dosage of 800 mg were recorded as 6.9 ± 4.2 µg/mL and 1.7 ± 0.3 µg/mL, respectively. Following a dosage of 800 mg to 1,800 mg administered orally on a daily basis, steady state levels of 1.57 ± 0.1 µg/mL and 3.9 µg/mL were recorded.

The amiodarone half-life is long and can take from 14 days to 110 days with a chronic oral dosage, however, it is typically within the range of 14 days to 59 days. Desethylamiodarone is the principal metabolite of amiodarone. This metabolite has been identified in the plasma and other tissues. It is also reported to have an extended half-life compared to amiodarone, for example, following a single dose of amiodarone the half-life is 10 hours and following chronic dosage of amiodarone the half-life is 60 to 90 days. The action of this metabolite is unknown. Amiodarone binds well to protein and it is believed to bind robustly to protein at 10 µg/ml concentration. It is understood that the majority of amiodarone is excreted via the gastrointestinal tract and liver by biliary excretion. There is the possibility of hepatic recirculation.

The evident volume of distribution following amiodarone administered orally at a dosage of 200 mg to 400 mg is 6.31 ± 4.93 L/kg. Amiodarone tends to accrue in adipose tissue and in

decidedly perfused organs, for example, adrenals, bone marrow, heart, kidney, liver, lung, pancreas, and spleen. Within packed red blood cells, the amiodarone concentration is approximately 60% of that in plasma.

5.3 Preclinical Safety Data

In chronic toxicity studies, amiodarone led to pulmonary damage (fibrosis, phospholipidosis; in hamsters, rats and dogs). Pulmonary toxicity appears to result from radical formation and perturbation of cellular energy production. In addition, amiodarone caused liver damage in rats. Regarding the genotoxicity aspects the in vitro Ames test and in vivo mouse bone marrow micronucleus test have been conducted. Both studies yielded negative results.

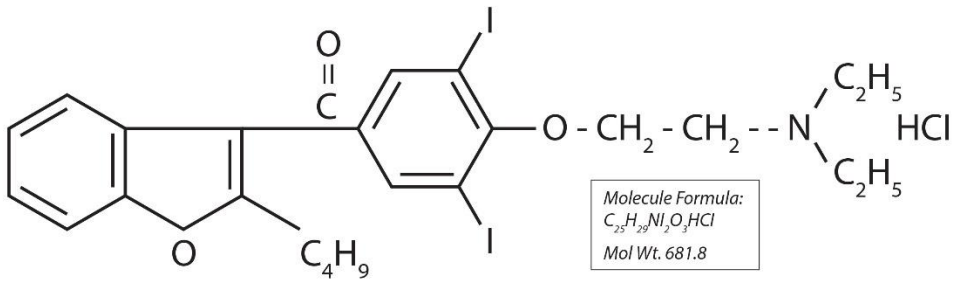
In a 2-years carcinogenicity study in rats, amiodarone caused an increase in thyroid follicular tumours (adenomas and/or carcinomas) in both sexes at clinical relevant exposures. Since mutagenicity findings were negative, an epigenic rather than genotoxic mechanism is proposed for this type of tumour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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol, hydrochloric acid, polysorbate 80, sodium hydroxide, water for injections

The chemical structure of amiodarone hydrochloride is shown below:



6.2 Incompatibilities

Lodi concentrate for infusion is incompatible with saline solution and may only be administered in a 5% w/v Glucose intravenous infusion.

In the presence of amiodarone the use of administration equipment containing softening agents such as DEHP (di-2-ethylhexyl phthalate) may cause DEHP to leach into the solution. In order to minimise patient exposure to DEHP, diluted amiodarone solutions for infusion should be administered through sets that do not contain DEHP, such as polyolefin (PE, PP) or glass sets. No other agents may be added to amiodarone infusions.

Lodi concentrate for infusion must not be mixed with other medicinal products except those mentioned above.

6.3 Shelf Life
Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage
Store at or below 25°C. Do not refrigerate. Do not freeze. Protect from light.

Keep the ampoules in the outer carton in order to protect from light. Lodi Concentrate for Infusion is intended for single dose only. Any unused solution should be discarded immediately after initial use.

6.5 Nature and contents of container
Injection, 150 mg / 3 mL in packs of five ampoules.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE
Prescription medicine

8 SPONSOR
REX Medical Limited
PO Box 18-119, Glen Innes
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Telephone: (09) 574 6060
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9 DATE OF FIRST APPROVAL
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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
1	Corrected in line with data sheet template