Very rare
Severe bradycardia (in cases of sinus node dysfunction and in the elderly) or (more rarely) sinus arrest: this may necessitate discontinuation of the treatment.
- Occurrence of new - and exacerbation of existing - arrhythmias, including atypical ventricular tachycardias (Torsades de Pointes).
- Conduction disturbances (sinoatrial block, AV block).
Vascular disorders
Common
- Hypotension and increased heart rate immediately following injection. These are generally moderate and transient in nature. Cases of severe hypotension or shock have been reported following overdose or too rapid administration (bolus injection).
Very rare
- Hot Flushes.
Respiratory, thoracic and mediastinal disorders
Very rare
- Interstitial pneumonitis.
- Acute ARDS (adult respiratory distress syndrome), sometimes with fatal sequelae.
Gastrointestinal disorders
Very rare
- Nausea.
Hepatobiliary disorders
Very rare
- A mild to moderate increase in transaminase levels (1.5 to 3 times above normal) at the start of treatment, which is often transient in nature and resolves spontaneously upon lowering the dose.
- Acute liver function disorders, with increased serum transaminase and/or jaundice, including hepatic failure, sometimes with fatal sequelae.
Skin and subcutaneous tissue disorders
Very rare
- Sweating.
Not known
- Urticaria.
General disorders and administration site conditions
Common
- At the site of injection or infusion: pain, erythema, oedema, necrosis, extravasation, infiltration, inflammation, induration, thrombophlebitis, phlebitis, cellulitis, infection, pigmentation changes.
Rare
- The excipient benzyl alcohol may cause hypersensitivity reactions. A few rare cases with various clinical symptoms, indicative of hypersensitivity reactions, have been
reported: vasculitis, reduced renal function with a rise in creatinine levels, thrombocytopenia, anaphylaxis.

OVERDOSE AND TREATMENT:
There is no information regarding overdosage with intravenous amiodarone. In cases of acute overdose or too rapid intravenous administration, the following can be observed: nausea, vomiting, constipation, sweating, bradycardia and prolonged QT interval. Following substantial overdose, onset of hypotension, heart block and Torsades de Pointes should also be expected. In exceptional cases, hyperthyroidism may occur.
Following substantial overdose, prolonged ECG monitoring must be performed. Intensive care unit admission should be considered. Hypotension can be treated with infusion fluids or vasopressors. The use of alpha- or beta adrenergic agents or temporary pacing may be indicated. Class Ia and III antiarrhythmic agents should be avoided, as they are associated with QT interval prolongation and induction of Torsades de Pointes. Further treatment should be supportive and symptomatic.
Amiodarone and its metabolites cannot be dialysed.
Due to the pharmacokinetics of amiodarone, adequate and prolonged surveillance of the patient, particularly cardiac status, is recommended.

STORAGE CONDITION: Store at a temperature not exceeding 30°C. Do not refrigerate or freeze. Protect from light. Keep out of the reach of children.
Shelf Life: 24 months

INSTRUCTIONS AND SPECIAL PRECAUTION FOR HANDLING AND DISPOSAL:
All discarded items should be placed in an opaque plastic sealable container, double-bag and place in the trash.

DOSAGE FORM AND PACKAGING AVAILABLE (PACK SIZE):
3 mL USP Type I Clear Glass Ampoule (Box of 5's and 10's)

Foods, Drugs, Devices, and Cosmetics Act prohibit dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Patient should seek medical attention immediately at the first sign of any adverse drug reaction.

DRP-13159

DATE OF FIRST AUTHORIZATION: January 2023
DATE OF REVISION OF PACKAGE INSERT: N/A

MANUFACTURED BY:
SWISS PARENTERALS LTD. (BLOCK-B)
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SPPH-AMD150SI-IN01-01

AMIODARONE HYDROCHLORIDE

AMIODAL

50mg/mL (150mg/3mL)
Sterile Concentrate Solution for IV Infusion
Antiarrhythmic Agent

℞

COMPOSITION:
Each mL contains:
Amiodarone Hydrochloride, BP ..... 50 mg
Benzyl Alcohol, BP .....2% w/v

PRODUCT DESCRIPTION:
A clear, slightly yellowish solution

PHARMACODYNAMICSD AND PHARMACOKINETICS
PHARMACODYNAMICS:
Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class III
ATC code: C01B D01.
Amiodarone Hydrochloride is a product for the treatment of tachyarrhythmias and has complex pharmacological actions. Its effects are anti-adrenergic (partial alpha and beta blockers). It has haemodynamic effects (increased blood flow and systematic/coronary vasodilation). The drug reduces myocardial oxygen consumption and has been shown to have a sparing effect of rat myocardial ATP utilisation, with decreased oxidative processes. Amiodarone inhibits the metabolic and biochemical effects of catecholamines on the heart and inhibits Na+ and K+ activated ATP-ase.
Amiodarone is a di-iodinated benzofuran derivative and is classified as a class III antiarrhythmic agent owing to its ability to increase the cardiac action potential duration in both atrial and ventricular myocytes via block of cardiac K+ channels (mainly of the rapid component of the delayed rectifier K+ current, Ikr). Thus, it prolongs the refractory period of the action potential leading to depression of ectopies and re-entry-arrhythmias and to prolongation of the QTc interval in the ECG. Furthermore, amiodarone also blocks cardiac Na+ currents (class I effect) and Ca2+ currents (class IV effect). The latter may lead to slowing of conduction through the sinoatrial and atrioventricular nodes.
During long-term administration, amiodarone also seems to inhibit the trafficking of ion channels from the endoplasmic reticulum to the plasma membrane in cardiac myocytes, and these effects may contribute to the cardiac electrophysiological actions of amiodarone under chronic administration.
Furthermore, amiodarone is a non-competitive antagonist at both ß- and α-adrenoceptors and, therefore, has haemodynamic effects: dilatation of coronary arteries and peripheral vasodilation leading to a reduction of systemic blood pressure. Negative inotropic, negative chronotropic and negative dromotropic effects seem to be induced by the ßadrenergic antagonistic effects induced by Amiodarone.
Paediatric population:
No controlled paediatric studies have been undertaken. In published studies the safety of amiodarone was evaluated in 1118 paediatric patients with various arrhythmias. The following doses were used in paediatric clinical trials.
Oral
- Loading dose: 10 to 20 mg/kg/day for 7 to 10 days (or 500 mg/m2/day if expressed per square meter),
- Maintenance dose: the minimum effective dosage should be used; according to individual response, it may range between 5 to 10 mg/kg/day (or 250 mg/m2/day if expressed per square meter).
Intravenous
- Loading dose: 5 mg/kg body weight over 20 minutes to 2 hours,
- Maintenance dose: 10 to 15 mg/kg/day from few hours to several days.
If needed oral therapy may be initiated concomitantly at the usual loading dose.

PHARMACOKINETICS:
Pharmacokinetics of amiodarone is unusual and complex, and have not been completely elucidated.
Absorption following oral administration is variable and may be prolonged, with enterohepatic cycling. Themajor metabolite is desethylamiodarone. Amiodarone is highly protein bound > 95%). Renal excretion is minimal and faecal excretion is the major route. A study in both healthy volunteers and patients after intravenous administration of amiodarone reported that the calculated volumes of distribution and total blood clearance using a two compartment open model were similar for both groups. Elimination of amiodarone after intravenous injection appeared to be bi-exponential with a distribution phase lasting about 4 hours. The very high volume of distribution combined with a relatively low apparent volume for the central compartment suggests extensive tissue distribution. A bolus IV injection of 400mg gave a terminal T½ of approximately 11 hours.

INDICATIONS:
Amiodarone Hydrochloride is indicated for the treatment of serious cardiac arrhythmias, in cases where other therapies are not effective or contraindicated such as:
- Atrial arrhythmias, including atrial fibrillation or flutter
- AV nodal arrhythmias and AV reentrant tachycardia, e.g. as a manifestation of Wolff – Parkinson - White syndrome
- Life-threatening ventricular arrhythmias, including persistent or non-persistent ventricular tachycardia or episodes of ventricular fibrillation.

DOSAGE AND MODE OF ADMINISTRATION
DOSAGE
Loading dose:
Administer 5 mg per kg body weight in 250 ml 5% glucose solution over 20 minutes to 2 hours and repeat 2 - 3 times every 24 hours up to 1200 mg (approximately 15 mg/kg body weight) in up to 500 ml 5% glucose per 24 hours, the rate of infusion being adjusted on the basis of clinical response. The effect occurs within a few minutes and decreases gradually therefore it must be followed by a maintenance dose.
Maintenance dose:
10 - 20 mg per kg body weight in 5% glucose solution every 24 hours (on average 600 to 800 mg/ 24 hours up to a maximum of 1200 mg/ 24 hours corresponding to 4-5 ampoules, maximum 8 ampoules) for a few days. On account of the stability of the solution, do not use concentrations below 300 mg per 500 ml and do not add other medicinal products to the infusion fluid. To prevent local reactions (phlebitis), do not use concentrations exceeding 3 mg/ml. It is advisable to start with an oral maintenance dose on the first day of the infusion. Repeated or continuous infusions via peripheral veins may lead to local reactions (inflammation). Whenever repeated or continuous infusions are intended, administration via a central line is recommended.
Caution: When given by infusion amiodarone may reduce drop size. If appropriate, adjustments should be made to the rate of infusion.
Direct intravenous injection ("bolus"):

In extreme clinical emergency amiodarone hydrochloride may, at the discretion of the doctor, be given as a slow injection. Administer 5 mg per kg body weight over at least 3 minutes. The duration of injection should always be no less than 3 minutes except in cases of cardiopulmonary resuscitation of shock-resistant ventricular fibrillation. A second bolus injection must not be administered within 15 minutes of the first, even if the initial injection consisted of only one ampoule (risk of irreversible shock).
minutes of the first, even if the initial injection consisted of only one ampoule (risk of irreversible shock). Patients treated in this way must be carefully monitored, e.g. in an intensive care unit. Administer bolus injections only in an emergency and do not use any other medicinal products in the same syringe. The indicated dose of 5 mg per kg, given as a direct injection, must not be exceeded.
Cardiopulmonary resuscitation of shock-resistant ventricular fibrillation/pulseless ventricular tachycardia:
The starting dose is 300 mg (or 5 mg/kg body weight) diluted in 20 ml 5% glucose which should be given by rapid injection. An additional dose of 150 mg (or 2.5 mg/kg body weight) I.V. may be considered if ventricular fibrillation persists.
Pediatric population:
The safety and efficacy of amiodarone in children has not been established. Due to the presence of benzyl alcohol, amiodarone intravenous administration is contraindicated in
neonates, infants and children up to 3 years old.
Elderly:
As with all patients it is important that the minimum effective dose is used. Whilst there is no evidence that dosage requirements are different for this group of patients they may be more susceptible to bradycardia and conduction defects if too high a dose is employed. Particular attention should be paid to monitoring thyroid function.
Hepatic and renal impairment:
Although no dosage adjustment for patients with renal or hepatic abnormalities has been defined duringchronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients e.g. in an intensive care unit.
Change over from intravenous to oral therapy:
Start with an oral maintenance dose for amiodarone hydrochloride as soon as an adequate response has been obtained. Amiodarone hydrochloride I.V. should then be phased out gradually. In patients taking amiodarone concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day.

MODE OF ADMINISTRATION:
Route of administration: intravenous use.
Amiodarone hydrochloride should only be used when facilities exist for cardiac monitoring, defibrillation and cardiac pacing.
Via infusion:
Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion is intended for single dose use only. Any unused solution should be discarded immediately after initial use. Before use, the sterile concentrate should be visually inspected for clarity, particulate matter, discolouration and the integrity of the container. The solution should only be used if it is clear and the container is undamaged and intact. Prior to administration by intravenous infusion, Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion should be diluted according to directions with the recommended infusion fluid, 5% w/v Glucose Intravenous Infusion. One ampoule of Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion diluted as recommended in 250 ml of 5 % w/v Glucose Intravenous Infusion results in a concentration of 0.6 mg/ml of amiodarone hydrochloride.
Administer 5 mg per kg body weight in 250 ml of 5 % glucose solution over 20 minutes to 2 hours. On account of the stability of the solution, do not use concentrations below 300 mg per 500 ml and do not add other medicinal products to the infusion fluid Method of administration

WARNINGS AND PRECAUTIONS:
Amiodarone Hydrochloride must only be prescribed by competent specialists. Using Amiodarone Hydrochloride requires careful and regular monitoring of liver function tests, thyroid function, an ECG and a radiological examination of the thorax. Administration of direct I.V. injections (bolus injections) is discouraged due to the risk of hemodynamic effects, such as serious hypotension and cardiovascular collapse. Such injections should only be used in an emergency - within a coronary intensive care unit and under ECG monitoring - when therapeutic alternatives have failed. Repeated or continuous infusion via peripheral veins may lead to injection site reactions. When repeated or continuous infusion is anticipated, administration by a central venous catheter is recommended.
Anaesthesia: Before surgery, the anaesthetist should be informed that the patient is taking amiodarone.
Amiodarone hydrochloride should only be used with constant monitoring of ECG and arterial blood pressure. Amiodarone hydrochloride should be used with extreme caution - with haemodynamic
monitoring - in patients with severe pulmonary impairment, arterial hypotension or stable congestive
heart failure. Such patients must not be given a bolus injection (risk of exacerbation).
The indicated dose of 5 mg per kg, given as a direct injection, must not be exceeded. If the effect of this product is too strong (e.g. severe bradycardia), appropriate measures must be taken, i.e. use of a pacemaker or beta stimulation. Use of amiodarone hydrochloride is not a contraindication for subsequent application of external defibrillation. Amiodarone Hydrochloride 50 mg/ml Concentrate for Solution for Injection/Infusion contains benzyl alcohol (22.2 mg/ml). Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old. Adverse effects are mostly the result of excessive dosage. It is therefore advisable to use the lowest possible dosage, in order to minimise the extent and severity of adverse effects.
Endocrine disorders
Intravenous amiodarone hydrochloride may induce hyperthyroidism, particularly in patients with a personal history of thyroid disorders, patients from an iodine-deficient population or patients who are taking or have previously taken oral amiodarone. Serum usTSH level should be measured when thyroid dysfunction is suspected. In cases of confirmed hyperthyroidism, therapy with intravenous amiodarone should be discontinued. In severe cases, sometimes resulting in fatalities, individual emergency therapy with thyreostatic drugs and/or corticosteroids should be initiated.
Cardiac disorders
Amiodarone hydrochloride can cause the development of new cardiac arrhythmias or exacerbate existing ones (proarrhythmic effect), sometimes with fatal sequelae. However, in comparison with some other antiarrhythmic agents, the incidence of this effect seems to be less frequent. Caution should be exercised, especially in patients with heart failure or first degree AV block. Furthermore, Torsades de Pointes has been described, a polymorphic ventricular tachycardia associated with QT prolongation. This arrhythmia occurs particularly in patients with a severely prolonged QT interval and/or in combination with medicinal products that cause hypokalaemia, certain antiarrhythmic agents and certain other agents that affect repolarisation.
In the ECG T wave changes and possible U wave occurrence result from a prolongation of the repolarisation phase by amiodarone. As with some other antiarrhythmic agents, this phenomenon can lead to atypical ventricular tachycardias ("Torsades de Pointes") in exceptional cases. It is important, but difficult, to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of drug interactions and/or electrolytic disorders. Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances, amiodarone treatment should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.
Pulmonary disorders
Cases of pulmonary toxicity (interstitial pneumonitis), sometimes with fatal sequelae, have been reported during use of intravenous amiodarone. A chest X-ray and pulmonary function testing should be performed at the onset of dyspnoea (on exertion), independent of whether or not the dyspnoea is accompanied by any changes in the patient's general condition (tiredness, weight loss, fever). Undesirable pulmonary effects are generally reversible and resolve rapidly upon discontinuation of treatment. Corticosteroid treatment can possibly be considered. In most cases, clinical symptoms resolve within 3 to 4 weeks, followed by a less rapid normalisation of radiological and lung function tests (up to a few months).
Very rare 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

Hepatic disorders
Severe liver failure can occur within the first 24 hours after administration of I.V. amiodarone, sometimes with fatal sequelae. Therefore, close monitoring of transaminases is recommended from the outset of treatment

CONTRAINDICATIONS
- Due to the presence of benzyl alcohol, intravenous amiodarone is contraindicated in neonates, infants and children up to 3 years old.
- Severe respiratory failure, circulatory collapse, or severe arterial hypotension; hypotension, heart failure and cardiomyopathy are also contraindications when using Amiodarone Hydrochloride 50 mg/ml as a bolus injection.
- Evidence or history of thyroid dysfunction. Thyroid function tests should be performed where appropriate prior to therapy in all patients.
- Sinus bradycardia, sino-atrial heart block and sick sinus syndrome in patients without a pacemaker. In patients with severe conduction disturbances (high grade AV block, bifascicular or trifascicular block) or sinus node disease, amiodarone should be used only in specialized units in conjunction with a pacemaker.
- Concomitant use of medicinal products which prolong the QT interval.
The above contraindications do not apply to the use of amiodarone hydrochloride for cardiopulmonary resuscitation of shock-resistant ventricular fibrillation.

DRUG INTERACTIONS:
Use of amiodarone hydrochloride in combination with the following medicinal products is not recommended: beta-blockers, heart rate lowering calcium channel blockers (verapamil, diltiazem), stimulant laxatives capable of causing hypokalaemia, fluoroquinolones and HIV-protease inhibitors. In patients receiving amiodarone concomitantly with simvastatin, the dose of simvastatin should not exceed 20 mg/day.
Increased plasma levels of flecainide have been reported with co-administration of amiodarone. The flecainide dose should be reduced accordingly and the patient closely monitored. After cessation of therapy- a therapeutic concentration of amiodarone may remain in the blood serum for some weeks in case of a repeated intravenous administration because of the long half-life of amiodarone. After further reduction of the amiodarone level, arrhythmias can recur. Patients must be monitored regularly after stopping treatment.
Too high a dosage may lead to severe bradycardia and to conduction disturbances with the appearance of an idioventricular rhythm, particularly in elderly patients or during digitalis therapy. In these circumstances, amiodarone treatment should be withdrawn. If necessary, beta-adrenostimulants or glucagon may be given. Because of the long half-life of amiodarone, if bradycardia is severe and symptomatic the insertion of a pacemaker should be considered.

PREGNANCY AND LACTATION:
Pregnancy
Data on a limited number of exposed pregnancies are available. Amiodarone and N-desmethylamiodarone cross the placental barrier and achieve 10-25% of the maternal plasma concentrations in the infant. Most frequent complications include impaired growth, preterm birth and impaired function of the thyroid gland in newborn babies.
Hypothyroidism, bradycardia and prolonged QT intervals were observed in approximately 10 % of the newborn babies. In isolated cases an increased thyroid gland or cardiac murmurs were found. The malformation rate does not appear to be increased. However, the possibility of cardiac defects should be kept in mind. Therefore,
amiodarone must not be used during pregnancy unless clearly necessary and the real risk of reoccurrence of life threatening arrhythmias should be weighed against the possible hazard for the foetus. Given the long half-life of amiodarone, women of child-bearing age would need to plan for a pregnancy starting at least half a year after finishing therapy, in order to avoid exposure of the embryo/foetus during early pregnancy.
Lactation
The passage into mother's milk is proven for the active ingredient and for the active metabolite. If therapy is required during the lactation period, or if amiodarone was taken during pregnancy, breast-feeding should be stopped.
Fertility
Elevated serum levels of LH and FSH were found in male patients after long-term treatment indicating testicular dysfunctions.

ADVERSE DRUG REACTIONS:
The most common adverse drug effects reported with intravenous amiodarone hydrochloride are infusion phlebitis, bradycardia, and hypotension.
Frequency of the adverse reaction listed below is defined according to the following convention:
Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥ 1/10,000 to <1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders
- In patients taking amiodarone there have been incidental findings of bone marrow granulomas. The clinical significance of this is unknown.
Immune system disorders
Very rare
- Anaphylactic shock.
- Angioedema (there have been some reports of angioedema, although exact frequencies are not known).
Endocrine disorders
Very rare:
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Frequency not known
- Hyperthyroidism, sometimes fatal - Hypothyroidism
Nervous system disorders
Very rare
- Benign intracranial hypertension (pseudo-tumour cerebri).
- Headache.
Cardiac disorders
Common
- Dose-dependent bradycardia.