

הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך 10.2012

שם תכשיר באנגלית AMIODACORE INJ

מספר רישום 430423211

שם בעל הרישום sanofi aventis Israel ltd

טקסט שהוסף מסומן בצהוב, טקסט מחוק מסומן באדום עם קו חוצה, שינויים בניסוח מסומנים בירוק (יש להדגיש כי מוזכר כאן רק המידע הנוסף, מידע מלא ניתן למצוא בעלון המלא):

פרטים על השינויים המבוקשים		
טקסט חדש	טקסט נוכחי	פרק בעלון
<p>...</p> <p>• Due to the presence of benzyl alcohol, Amiodacore Injection is contraindicated in neonates, infants and children up to 3 years old Amiodacore Injection ampoules contain benzyl alcohol. There have been reports of fatal 'gaspings syndrome' in neonates (hypotension, bradycardia and cardiovascular collapse) following the administration of intravenous solution containing this preservative. Amiodacore Injection should not be given to neonates or premature babies unless the rhythm disturbance is life threatening and either resistant to other medication or alternative therapy is deemed inappropriate.</p> <p>....</p>		<p>4. CLINICAL PARTICULARS</p> <p>4.3 Contraindications</p>
<p>....</p> <p>The safety and efficacy of amiodarone in paediatric patients have not been established. Therefore, its use in paediatric patients is not recommended.</p> <p>Benzyl alcohol may cause toxic reactions and allergic reactions in infants and children up to 3 years old.</p> <p>Ampoules of injectable amiodarone contain benzyl alcohol (see section 1.4). There have been reports of fatal " gasping syndrome " in neonates (children less than one month of age) following the administration of intravenous solutions containing this preservative. Symptoms include a striking onset of gasping syndrome, hypotension, bradycardia, and cardio-vascular collapse.</p> <p>As benzyl alcohol may cross the placenta, solution for injection should be used with caution in pregnancy.</p> <p>....</p> <p>Dosage is approximately 5 mg/kg body-weight. Except</p>		<p>4.4 Special warnings and precautions for use</p>

<p>for cases of cardio- pulmonary resuscitation of shock resistant ventricular fibrillation, amiodarone should be injected over a minimum period of 3 minutes. Intravenous injection should not be repeated less than 15 minutes following the first injection even if the latter was only 1 ampoule (possible irreversible collapse).</p> <p>Do not mix other preparations in the same syringe. Do not inject other preparations in the same line. If amiodarone should be continued, this should be via intravenous infusion (see section 3).</p> <p>....</p> <p>Cardiac disorders:</p> <p>.....</p> <p>Amiodarone has a low pro-arrhythmic effect. Onsets of new arrhythmias or worsening of treated arrhythmias, sometimes fatal, have been reported. It is important, but difficult to differentiate a lack of efficacy of the drug from a proarrhythmic effect, whether or not this is associated with a worsening of the cardiac condition. Proarrhythmic effects generally occur in the context of QT prolonging factors such as drug interactions and/or electrolytic disorders (see sections 4.5 and 4.8). Despite QT interval prolongation, amiodarone exhibits a low torsadogenic activity.</p> <p>....</p> <p>Respiratory, thoracic and mediastinal disorders (see section 4.8):</p> <p>Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity such as interstitial pneumonitis. ...</p>		
<p>4.5.1 Pharmacodynamic interactions</p> <ul style="list-style-type: none"> • <u>Drugs inducing Torsade de Pointes or prolonging QT</u> <ul style="list-style-type: none"> - <u>Drugs inducing Torsade de Pointes</u> <p>Combined therapy with drugs that may induce “torsade de pointes” is contra-indicated (see section 4.3):</p> <ul style="list-style-type: none"> • antiarrhythmic agents such as Class Ia, sotalol, bepridil, • non-antiarrhythmic agents such as vincamine, some neuroleptic agents, cisapride, erythromycin IV, pentamidine (when parenterally administrated), as there is an increased risk of potentially lethal “torsade de pointes ”. 		<p>4.5 Interaction with other medicinal products and other forms of interaction</p>

<p>- <u>Drugs prolonging QT</u></p> <p>Co-administration of amiodarone with drugs 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 (see Section 4.4) and patients should be monitored for QT prolongation.</p> <p>...</p> <ul style="list-style-type: none"> • <u>Drugs lowering heart rate or causing automaticity or conduction disorders</u> <p>Combined therapy with these drugs is not recommended.</p> <p>.....</p> <ul style="list-style-type: none"> • <u>Agents which may induce hypokalaemia:</u> <p>- Combined therapy with the following drugs is not recommended:</p> <p>.....</p> <ul style="list-style-type: none"> • <u>General anaesthesia (see section 4.4 and section 4.8):</u> <p>.....</p> <p>A few cases of adult respiratory distress syndrome, most often in the period immediately after surgery, have been observed. Very rare 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.</p>		
<p>4.5.2 Effect of Amiodacore injection on other medical products</p> <p>Amiodarone and/or its metabolite, desethylamiodarone, inhibit CYP1A1, CYP1A2, CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and may increase exposure of their substrates.</p> <p>Due to the long half life of amiodarone, interactions may be observed for several months after discontinuation of amiodarone.</p> <ul style="list-style-type: none"> • <u>PgP substrates</u> <p>Amiodarone is a P-gp inhibitor. Co administration with P-gp substrates is expected to result in an increase of their exposure.</p> <p>- <u>Digitalis</u></p>		

~~Administration of Amiodacore to a patient already receiving digoxin will bring about an increase in the plasma digoxin concentration and thus precipitate symptoms and signs associated with high digoxin levels. Clinical, ECG and biological monitoring is recommended and digoxin dosage should be halved. A synergistic effect on heart rate and atrioventricular conduction is also possible.~~

Disturbances in automaticity (excessive bradycardia) and atrioventricular conduction (synergistic action) may occur; in addition, an increase in plasma digoxin concentrations is possible due to the decrease in digoxin clearance.

ECG, and digoxin plasma levels should be monitored, and patients should be observed for clinical signs of digitalis toxicity. It may be necessary to adjust dosage of digitalis treatment.

- Dabigatran

Caution should be exercised when amiodarone is co administered with dabigatran due to the risk of bleeding. It may be necessary to adjust the dosage of dabigatran as per its label.

• CYP 2C9 substrates

~~Amiodarone raises the plasma concentrations of oral anticoagulants (warfarin) and phenytoin by inhibition of CYP 2C9. The dose of warfarin should be reduced accordingly. More frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. Phenytoin dosage should be reduced if signs of overdosage appear, and plasma levels may be measured.~~

Amiodarone raises the concentrations of CYP 2C9 substrates such as warfarin or phenytoin by inhibition of the cytochrome P450 2C9.

- Warfarin

The combination of warfarin with amiodarone may exacerbate the effect of the oral anticoagulant thus increasing the risk of bleeding. It is necessary to monitor prothrombin (INR) levels more regularly and to adjust oral doses of anticoagulant agents both during treatment with amiodarone and after discontinuation of amiodarone treatment.

- Phenytoin

The combination of phenytoin with amiodarone may lead to phenytoin overdosage, resulting in neurological signs. Clinical monitoring should be

<p>undertaken and phenytoin dosage should be reduced as soon as overdosage signs appear; phenytoin plasma levels should be determined.</p> <ul style="list-style-type: none"> • CYP 2D6 substrates <p>.....</p> <ul style="list-style-type: none"> • Drugs metabolized by cytochrome CYP P450 3A4 substrates <p>.....</p> <ul style="list-style-type: none"> • Other drugs metabolized by cytochrome P450 3A4: examples of such drugs are lidocaine, tacrolimus, sildenafil, fentanyl, midazolam, triazolam, dihydroergotamine, and ergotamine and colchicine. <p><u>Interaction with substrates of other CYP 450 isoenzymes</u></p> <p>In vitro studies show that amiodarone also has the potential to inhibit CYP 1A2, CYP 2C19 and CYP 2D6 through its main metabolite. When co-administered, amiodarone would be expected to increase the plasma concentration of drugs whose metabolism is dependent upon CYP 1A2, CYP 2C19 and CYP 2D6.</p>		
<p>4.5.3 Effect of other products on Amiodacore injection</p> <p>Grapefruit juice inhibits cytochrome P450 3A4 and may increase the plasma concentration of amiodarone. Grapefruit juice should be avoided during treatment with oral amiodarone.</p> <p>CYP3A4 inhibitors and CYP2C8 inhibitors may have a potential to inhibit amiodarone metabolism and to increase its exposure.</p> <p>It is recommended to avoid CYP 3A4 inhibitors (e.g grapefruit juice and certain medicinal products) during treatment with amiodarone.</p>		
<p>...</p> <p>Cardiac disorders:</p> <p>....</p> <ul style="list-style-type: none"> - Onset of or worsening of arrhythmia, sometimes followed by cardiac arrest (see sections 4.4 and 4.5). • Frequency not known: Torsade de pointes (see sections 4.4 and 4.5). <p>....</p> <p>Immune system disorders:</p>		<p>4.8 Undesirable effects</p>

.... • Frequency not known: Angioedema Angioneurotic oedema (Quincke's Oedema)		
..... Amiodarone is metabolized 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 (an OCT 2 substrate) In vivo data describe amiodarone interactions on CYP3A4, CYP2C9, CYP2D6 and P-gp substrates.		5. PHARMACOLOGICAL PROPERTIES 5.2 Pharmacokinetic properties

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24.10.12 העלון, שבו מסומנים השינויים המבוקשים הועבר בדואר אלקטרוני בתאריך

☐ קיים עלון לצרכן והוא מעודכן בהתאם:

☐ אסמכתא לבקשה: CCDS 14, CCDS 15, Benzyl Alcohol warning

☐ השינויים הנ"ל **טרם** אושרו על ידי רשויות הבריאות באנגליה

☐ אני, הרוקחת הממונה של חברת סאנופי אוונטיס ישראל בע"מ מצהירה בזה כי קיימים שינויים נוספים בעלון - השינויים בטופס זה הינם השינויים העיקריים שנעשו.

חתימת הרוקח הממונה