

## הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך 11/05/2015

שם תכשיר באנגלית ומספר הרישום

Tambocor Injection 106-41-23294-00

שם בעל הרישום מגאפארם בע"מ

טופס זה מיועד לפרוט ההחמרות בלבד !

### ההחמרות המבוקשות בעלון לרופא

פרק בעלון	טקסט נוכחי	טקסט חדש
Posology and method of administration	<b>Children:</b> Tambocor is not recommended in children under 12	<b>Children:</b> Tambocor is not recommended in children under 12, as there is insufficient evidence of its use in this age group.
Contraindications	<p>Tambocor is contra-indicated in cardiac failure and in patients with a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.</p> <p>It is also contra-indicated in patients with long standing atrial fibrillation in whom there has been no attempt to convert to sinus rhythm, and in patients with haemodynamically significant valvular heart disease.</p> <p>Unless pacing rescue is available, Tambocor should not be given to patients with sinus node dysfunction, atrial conduction defects, second degree or greater atrioventricular block, bundle branch block or distal block.</p>	<p>Hypersensitivity to flecainide or to any of the excipients.</p> <p>Tambocor is contra-indicated in cardiac failure and in patients with a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.</p> <p>Flecainide is contra-indicated in the presence of cardiogenic shock.</p> <p>It is also contra-indicated in patients with long standing atrial fibrillation in whom there has been no attempt to convert to sinus rhythm, and in patients with haemodynamically significant valvular heart disease.</p> <p>Known Brugada syndrome.</p> <p>Unless pacing rescue is available, Tambocor should not be given to patients with sinus node dysfunction, atrial conduction defects, second degree or greater atrioventricular block, bundle branch block or distal block.</p>
Special warnings and precautions for use	Electrolyte disturbances (e.g. hypo- and hyperkalaemia) should be corrected before using Tambocor (see section 4.5 for some drugs causing electrolyte	Electrolyte disturbances (e.g. hypo- and hyperkalaemia) should be corrected before using Tambocor (see section 4.5 for some drugs causing electrolyte

<p>disturbances).</p> <p>Since flecainide elimination from the plasma can be markedly slower in patients with significant hepatic impairment, flecainide should not be used in such patients unless the potential benefits clearly outweigh the risks. Plasma level monitoring is strongly recommended in these circumstances.</p> <p>Tambocor is known to increase endocardial pacing thresholds - ie to decrease endocardial pacing sensitivity. This effect is reversible and is more marked on the acute pacing threshold than on the chronic.</p> <p>Tambocor should thus be used with caution in all patients with permanent pacemakers or temporary pacing electrodes, and should not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitable pacing rescue is available.</p> <p>Generally, a doubling of either pulse width or voltage is sufficient to regain capture, but it may be difficult to obtain ventricular thresholds less than 1 Volt at initial implantation in the presence of Tambocor.</p> <p>The minor negative inotropic effect of flecainide may assume importance in patients predisposed to cardiac failure. Difficulty has been experienced in defibrillating some patients. Most of the cases reported had pre-existing heart disease with cardiac enlargement, a history of myocardial infarction, arterio-sclerotic heart disease and cardiac failure.</p> <p>Tambocor has been shown to increase mortality risk of post-myocardial infarction patients with asymptomatic ventricular arrhythmia.</p> <p>Tambocor, like other antiarrhythmics, may cause proarrhythmic effects, i.e. it may cause the appearance of a</p>	<p>disturbances).</p> <p>Since flecainide elimination from the plasma can be markedly slower in patients with significant hepatic impairment, flecainide should not be used in such patients unless the potential benefits clearly outweigh the risks. Plasma level monitoring is strongly recommended in these circumstances.</p> <p>Tambocor is known to increase endocardial pacing thresholds - ie to decrease endocardial pacing sensitivity. This effect is reversible and is more marked on the acute pacing threshold than on the chronic.</p> <p>Tambocor should thus be used with caution in all patients with permanent pacemakers or temporary pacing electrodes, and should not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitable pacing rescue is available.</p> <p>The minor negative inotropic effect of flecainide may assume importance in patients predisposed to cardiac failure. Difficulty has been experienced in defibrillating some patients. Most of the cases reported had pre-existing heart disease with cardiac enlargement, a history of myocardial infarction, arterio-sclerotic heart disease and cardiac failure.</p>	
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more severe type of arrhythmia, increase the frequency of an existing arrhythmia or the severity of the symptoms (see 4.8).

Tambocor should be used with caution in patients with impaired renal function (creatinine clearance  $\leq 35$  ml/min/1.73 m<sup>2</sup>) and therapeutic drug monitoring is recommended.

The rate of flecainide elimination from plasma may be reduced in the elderly. This should be taken into consideration when making dose adjustments.

Tambocor is not recommended in children under 12 years of age, as there is insufficient evidence of its use in this age group.

Severe bradycardia or pronounced hypotension should be corrected before using flecainide.

Tambocor should be avoided in patients with structural organic heart disease or abnormal left ventricular function.

Tambocor should be used with caution in patients with acute onset of atrial fibrillation following cardiac surgery.

Treatment for patients with other indications should continue to be initiated in hospital. Intravenous treatment with flecainide should be initiated in hospital.

Continuous ECG monitoring is recommended in all patients receiving bolus injection.

Tambocor prolongs the QT interval and widens the QRS complex by 12-20 %. The effect on the JT interval is insignificant.

A Brugada syndrome may be unmasked due to flecainide therapy. In the case of development of ECG changes during treatment with flecainide that may indicate Brugada syndrome, consideration to discontinue the treatment should be made.

Tambocor should be used with caution in patients with acute onset of atrial fibrillation following cardiac surgery.

<p>In a large scale, placebo-controlled clinical trial in post-myocardial infarction patients with asymptomatic ventricular arrhythmia, oral flecainide was associated with a 2.2 fold higher incidence of mortality or non-fatal cardiac arrest as compared with its matching placebo. In that same study, an even higher incidence of mortality was observed in flecainide-treated patients with more than one myocardial infarction. Comparable placebo-controlled clinical trials have not been done to determine if flecainide is associated with higher risk of mortality in other patient groups.</p> <p>Dairy products (milk, infant formula and possibly yoghurt) may reduce the absorption of flecainide in children and infants. Flecainide is not approved for use in children below the age of 12 years, however flecainide toxicity has been reported during treatment with flecainide in children who reduced their intake of milk, and in infants who were switched from milk formula to dextrose feedings.</p> <p>Flecainide as a narrow therapeutic index drug requires caution and close monitoring when switching a patient to a different formulation.</p> <p>For further warnings and precautions please refer to section 4.5 (Interaction).</p>		
<p>Cardiac glycosides; Flecainide can cause the plasma <i>digoxin</i> level to rise by about 15%, which is unlikely to be of clinical significance for patients with plasma levels in the therapeutic range. It is recommended that the <i>digoxin</i> plasma level in digitalised patients should be measured not less than six hours after any <i>digoxin</i> dose, before or after administration of flecainide.</p> <p>Anti-depressants: <i>fluoxetine</i>, <i>paroxetine</i> and other antidepressants increases plasma flecainide concentration; increased risk of arrhythmias with <i>tricyclics</i>; manufacturer of <i>reboxetine</i> advises</p>	<p>Cardiac glycosides; Flecainide can cause the plasma <i>digoxin</i> level to rise by about 15%, It is recommended that the <i>digoxin</i> plasma level in digitalised patients should be measured not less than six hours after any <i>digoxin</i> dose, before or after administration of flecainide.</p> <p>Anti-depressants: and other antidepressants increases plasma flecainide concentration; increased risk of arrhythmias with <i>tricyclics</i>; manufacturer of <i>reboxetine</i> advises caution.</p>	<p><b>Interaction with other medicinal products and other forms of interaction</b></p>

<p>caution.</p> <p>Life-threatening or even lethal adverse events due to interactions causing increased plasma concentrations may occur (see 4.9). Flecainide is metabolised by CYP2D6 to a large extent, and concurrent use of drugs inhibiting (e.g. antidepressants, neuroleptics, propranolol, ritonavir, some antihistamines) or inducing (e.g. phenytoin, phenobarbital, carbamazepine) this iso-enzyme can increase or decrease plasma concentrations of flecainide, respectively (see below).</p> <p>An increase of plasma levels may also result from renal impairment due to a reduced clearance of flecainide</p> <p>Hypokalaemia but also hyperkalaemia or other electrolyte disturbances should be corrected before administration of flecainide. Hypokalaemia may result from the concomitant use of diuretics, corticosteroids or laxatives.</p> <p>H2 antihistamines (for the treatment of gastric ulcers): <i>cimetidine</i> inhibits metabolism of flecainide. In healthy subjects receiving <i>cimetidine</i> (1g daily) for one week, plasma flecainide levels increased by about 30% and the half-life increased by about 10%.</p> <p>Anti-smoking aids: Co-administration of <i>bupropion</i> with drugs that are metabolized by CYP2D6 isoenzyme including flecainide, should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If <i>bupropion</i> is added to the treatment regimen of a patient already receiving flecainide, the need to decrease the dose of the original medication should be considered.</p>	<p>H2 antihistamines (for the treatment of gastric ulcers): <i>cimetidine</i> inhibits metabolism of flecainide. In healthy subjects receiving <i>cimetidine</i> (1g daily) for one week, plasma flecainide levels increased by about 30%</p> <p>Anti-smoking aids: Co-administration of <i>bupropion</i> with drugs that are metabolized by CYP2D6 isoenzyme including flecainide, If <i>bupropion</i> is added to the treatment regimen of a patient already receiving</p>	
<p>Pregnancy information</p> <p>There is no evidence as to drug safety in human pregnancy. In New Zealand White rabbits, high doses of flecainide caused some foetal abnormalities, but</p>	<p>Pregnancy information</p> <p>Data have shown that flecainide crosses the placenta to the foetus in patients taking flecainide during pregnancy.</p>	<p><b>Fertility, Pregnancy and Lactation</b></p>

<p>these effects were not seen in Dutch Belted rabbits or rats (see 5.3). The relevance of these findings to humans has not been established. Data have shown that flecainide crosses the placenta to the foetus in patients taking flecainide during pregnancy. Flecainide should only be used in pregnancy if the benefit outweighs the risks.</p> <p>Lactation information</p> <p>Flecainide is excreted in human milk. Plasma concentrations obtained in a nursing infant are 5-10 times lower than therapeutic drug concentrations (see 5.2). Although the risk of adverse effects to the nursing infant is very small, flecainide should only be used during lactation if the benefit outweighs the risks.</p>	<p>Flecainide should only be used in pregnancy if the benefit outweighs the risks.</p> <p>Lactation information</p> <p>Flecainide is excreted in human milk. (see 5.2). Although the risk of adverse effects to the nursing infant is very small,</p>	
<p>Tambocor 10mg/ml Injection or infusion has no or negligible influence on the ability to drive and use machines. However, driving ability, operation of machinery and work without a secure fit may be affected by adverse reactions such as dizziness and visual disturbances (if present)</p>	<p>----</p>	<p><b>Effects on ability to drive and use machines</b></p>
<p><b>Nervous system disorders:</b>  <i>Very common:</i> dizziness, which is usually transient  <i>Rare:</i> paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, convulsion, dyskinesia</p> <p><b>Cardiac disorders:</b>  <i>Common:</i> Proarrhythmia (most likely in patients with structural heart disease and/or significant left ventricular impairment).  <i>Frequency not known</i> (cannot be estimated from the available data). Dose-related increases in PR and QRS intervals may occur (see 4.4). Altered pacing threshold (see 4.4).</p> <p><i>Uncommon:</i> Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate.</p>	<p><b>Nervous system disorders:</b>  <i>Very common:</i> dizziness, which is usually transient  <i>Rare:</i> paraesthesia, ataxia, hypoaesthesia, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, convulsion, dyskinesia</p> <p><b>Cardiac disorders:</b>  <i>Common:</i> Proarrhythmia (most likely in patients with structural heart disease and/or significant left ventricular impairment).</p> <p><i>Uncommon:</i> Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate.</p>	<p><b>Undesirable effects</b></p>

<p><i>Frequency not known</i> (cannot be estimated from the available data): atrioventricular block-second- degree and atrioventricular block third degree, cardiac arrest, bradycardia, cardiac failure/ cardiac failure congestive, chest pain, hypotension, myocardial infarction, palpitations, sinus pause or arrest, and tachycardia (AT or VT) or ventricular fibrillation. Demasking of a pre-existing Brugada syndrome.</p> <p><b>Respiratory, thoracic and mediastinal disorders:</b> <i>Common:</i> dyspnoea <i>Rare:</i> pneumonitis <i>Frequency not known</i> (cannot be estimated from the available data): pulmonary fibrosis, interstitial lung disease</p> <p><b>Skin and subcutaneous tissue disorders:</b> <i>Uncommon:</i> dermatitis allergic, including rash, alopecia <i>Rare:</i> serious urticaria <i>Very rare:</i> photosensitivity reaction</p>	<p><i>Frequency not known</i> (cannot be estimated from the available data): atrioventricular block-second- degree and atrioventricular block third degree, cardiac arrest, bradycardia, cardiac failure/ cardiac failure congestive, chest pain, hypotension, myocardial infarction, palpitations, sinus pause or arrest, and tachycardia (AT or VT)</p> <p><b>Respiratory, thoracic and mediastinal disorders:</b> <i>Common:</i> dyspnoea <i>Rare:</i> pneumonitis</p> <p><b>Skin and subcutaneous tissue disorders:</b> <i>Uncommon:</i> dermatitis allergic, including rash, <i>Rare:</i> serious urticaria <i>Very rare:</i> photosensitivity reaction</p>	
<p>Overdosage with flecainide is a potentially life-threatening medical emergency. Increased drug susceptibility and plasma levels exceeding therapeutic levels may also result from drug interaction (see 4.5). No specific antidote is known. There is no known way to rapidly remove flecainide from the system. Neither dialysis nor haemoperfusion is effective.</p> <p>Treatment should be supportive and may include removal of unabsorbed drug from the GI tract. Further measures may include inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol as well as mechanical ventilation and circulatory assistance (e.g. ballon pumping). Temporarily inserting a transvenous pacemaker in the event of conduction block should be considered. Assuming a plasma half-life of approximately 20 h, these supportive treatments may need to be continued for an extended period of time. Forced</p>	<p>No specific antidote is known. There is no known way to rapidly remove flecainide from the system. Neither dialysis nor haemoperfusion is effective.</p> <p>Further measures may include inotropic agents as well as mechanical ventilation and circulatory assistance (e.g. ballon pumping). Temporarily inserting a transvenous pacemaker in the event of conduction block should be considered.</p>	<p><b>Overdose</b></p>

diuresis with acidification of the urine theoretically promotes drug excretion.		
One rabbit tribe showed teratogenicity and embryotoxicity under flecainide. This effect was neither present in other rabbit tribes nor in rats or mice. Prolongation of gestation was seen in rats under a dose of 50 mg/kg. No effects on fertility were observed. No human data concerning pregnancy and lactation are available.	----	<b>Preclinical safety data</b>
Dilution: When necessary Tambocor injection should be diluted with, or injected into, sterile solutions of 5% dextrose. If chloride containing solutions, such as sodium chloride or Ringer's lactate are used, the injection should be added to a volume of not less than 500 ml, otherwise a precipitate will form. For single use only.	---	<b>Special precautions for disposal and other handling</b>

מצ"ב העלון, שבו מסומנות החמרות המבוקשות **על רקע צהוב**.  
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה.  
הועבר בדואר אלקטרוני בתאריך 11/05/2015