Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tambocor 10 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg flecainide acetate.

Each 15 ml ampoule contains 150 mg flecainide acetate.

Excipients: contains 38mg of sodium per ampoule.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

It is recommended that treatment with Tambocor should be initiated in hospitals.

'Tambocor' injection is indicated when rapid control of the following arrhythmias is the main clinical requirement.

a) Ventricular tachyarrhythmias.
b) AV nodal reciprocating tachycardia when patients have been unresponsive to beta-blockers or calcium channel blockers and in the absence of left ventricular dysfunction (See 4.3, Contra-indications).
c) Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways in the absence of left-ventricular dysfunction (See 4.3, Contraindications).
d) Atrial fibrillation and atrial flutter when treatment need has been established and in the absence of left ventricular dysfunction (See 4.3, Contra-indications).

4.2 Posology and method of administration

Initiation of therapy should take place in the hospital environment with ECG monitoring. ECG monitoring should be maintained during intravenous infusion.

Adults Only:
a) Bolus injection: Tambocor can be given in an emergency or for rapid effect by a slow injection of 2mg/kg over not less than ten minutes, or in divided doses. If preferred, the dose may be diluted with 5% dextrose and given as a mini-infusion. Continuous ECG monitoring is recommended in all patients receiving the bolus dose. The injection should be stopped when there is control of the arrhythmia.

It is recommended that Tambocor should be administered more slowly to patients in sustained ventricular tachycardia, with careful monitoring of the electrocardiogram. Similar caution should apply to patients with a history of cardiac failure, who may become decompensated during the administration. For such patients it is recommended that the initial dose is given over 30 minutes.

The maximum recommended bolus dose is 150 mg
b) Intravenous infusion: When prolonged parenteral administration is required, it is recommended that therapy is initiated by slow injection of 2 mg/kg over 30 minutes as above and continued by intravenous infusion at the following rates:
First hour: 1.5 mg/kg per hour.
Second and later hours: 0.1 - 0.25 mg/kg per hour.

It is recommended that the infusion duration should not exceed 24 hours. However, where this is considered necessary, or for patients receiving the upper end of the dose range, plasma level monitoring is strongly recommended.

The maximum cumulative dose given in the first 24 hours should not exceed 600 mg. In patients with severe renal impairment (creatinine clearance of less than 35ml/min/1.73 sq m), each of the above dosage recommendations should be reduced by half.

Transition to oral dosing should be accomplished as soon as possible by stopping the infusion and administering the first required oral dose. Oral maintenance is then continued as indicated in the relevant oral dosage instructions.

Children: Tambocor is not recommended in children under 18, as there is insufficient evidence of its use in this age group.

Older Patients: The rate of flecainide elimination from plasma may be reduced in older people. This should be taken into consideration when making dose adjustments.

Plasma levels: Based on PVC suppression, it appears that plasma levels of 200-1000ng/ml may be needed to obtain the maximum therapeutic effect. Plasma levels above 700-1000ng/ml are associated with increased likelihood of adverse experiences.

Dosage in impaired renal function: In patients with significant renal impairment (creatinine clearance of 35 ml/min/1.73 sqs.m. or less) the maximum initial dosage should be 100 mg daily (or 50 mg twice daily).

When used in such patients, frequent plasma level monitoring is strongly recommended.

Significant hepatic impairment: 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 outweigh the risks. Plasma level monitoring is recommended.

4.3 Contraindications

Hypersensitivity to flecainide or to any of the excipients.

Tambocor is contra-indicated in patients with left ventricular dysfunction or heart failure, regardless of the type of arrhythmia, and in patients with a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.

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. Use in patients with asymptomatic or non-life threatening symptomatic arrhythmias.

Unless pacing rescue is available, Tambocor should not be given to patients with sinus node dysfunction, atrial conduction defects, second degree or third degree atrio-ventricular block, bundle branch block or distal block.

Use in patients with significant electrolyte imbalance.

Known Brugada syndrome.

Tambocor is contra-indicated in patients with known hypersensitivity to amide drugs.

Tambocor is contra-indicated in the presence of cardiogenic shock.

Use with other Class 1 anti-arrhythmics.

4.4 Special warnings and precautions for use

Intravenous treatment with flecainide should be initiated in hospital

Flecainide has been shown to increase mortality risk of post-myocardial infarction patients with asymptomatic ventricular arrhythmia.

Flecainide, like other antiarrhythmics, may cause proarrhythmic effects, i.e. it may cause the appearance of a more severe type of arrhythmia, increase the frequency of an existing arrhythmia or the severity of the symptoms (see section 4.8, Undesirable effects).

Flecainide should be avoided in patients with structural heart disease or abnormal left ventricular functions (see section 4.8, Undesirable effects).

Treatment for patients with ventricular arrhythmias should be initiated in hospital.

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

Flecainide 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 the development of ECG changes during treatment with flecainide that may indicate Brugada syndrome, consideration to discontinue the treatment should be made.

Electrolyte disturbances (e.g hypo- and hyperkalaemia) should be corrected before using Tambocor, and should be checked during therapy particularly if diuretics are being administered.

Severe bradycardia or pronounced hypotension should be corrected before using flecainide

This product should be used with caution in patients with severe hepatic disease.
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.

Flecainide should be used with caution in patients with impaired renal function (creatinine clearance ≤ 35ml/min/1.73 m^2) and therapeutic drug monitoring is recommended as increase of plasma levels may also result from renal impairment due to a reduced clearance of flecainide.

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

Tambocor is known to increase endocardial pacing thresholds – i.e. to decrease endocardial pacing sensitivity. This effect is reversible and is more marked on the acute pacing threshold than on the chronic. 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.

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.

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 preexisting heart disease with cardiac enlargement, a history of myocardial infarction, arterio-sclerotic heart disease and cardiac failure.

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

Tambocor was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centre, randomised, double-blind study in patients with asymptomatic nonlife- threatening arrhythmias who had had a myocardial infarction more than six days, but less than two years, previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with Tambocor compared with that seen in a carefully matched placebo-treated group. This rate was 16/316 (5.1%) for Tambocor and 7/309 (2.3%) for its matched placebo. The average duration of treatment with Tambocor in this study was 10 months. It was noted that the increased risk from sudden cardiac death occurred in patients with a history of multiple previous myocardial infarction, usually with poor ventricular function.

Dairy products (milk, infant formula and possible 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.

Flecainide as a narrow therapeutic index drug requires caution and close monitoring when switching a patient to a different formulation

Excipients: This medicinal product contains 38 mg sodium per ampoule. This is equivalent to 1.9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Flecainide is a class I anti-arrhythmic and interactions are possible with other anti-arrhythmic drugs where additive effects may occur or where drugs interfere with the metabolism of flecainide. The following known categories of drugs may interact with flecainide:

Cardiac glycosides: Flecainide can cause the plasma *digoxin* 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 *digoxin* plasma level in digitalised patients should be measured not less than six hours after any *digoxin* dose, before or after administration of flecainide.

Class II anti-arrhythmics: the possibility of additive negative inotropic effects of beta-blockers and other cardiac depressants, such as verapamil, with flecainide should be recognised.

Class III anti-arrhythmics: when flecainide is given in the presence of *amiodarone*, the usual flecainide dosage should be reduced by 50% and the patient monitored closely for adverse effects. Plasma level monitoring is strongly recommended in these circumstances.

Class IV anti-arrhythmics: use of flecainide with other calcium channel blockers, e.g. verapamil, should be considered with caution.

Life-threatening or even lethal adverse events due to interactions causing increased plasma concentrations may occur (see section 4.9, Overdose). Flecainide is metabolized 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).

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.

Anti-depressants; *fluoxetine, paroxetine and other antidepressants* increases plasma flecainide concentration; increased risk of arrhythmias with *tricyclics*; manufacturer of *reboxetine* advises caution.

Anti-epileptics: limited data in patients receiving known enzyme inducers (*phenytoin, Phenobarbital, carbamazepine*) indicate only a 30% increase in the rate of flecainide elimination.

Anti-psychotics: *clozapine* – increased risk of arrhythmias.

Anti-histamines: increased risk of ventricular arrhythmias with *mizolastine* and *terfenadine* (avoid concomitant use).

Anti-malarials: *quinine* increases plasma concentration of flecainide.

Antivirals: plasma concentration increased by *ritonavir*, (increased risk of ventricular arrhythmias (avoid concomitant use).

Antifungals: Terbinafine may increase plasma concentrations of flecainide resulting from its inhibition of CYP2D6 activity.

H2 antihistamines (for the treatment of gastric ulcers): The H2 agonist *cimetidine* inhibits the metabolism of flecainide. In healthy subjects receiving *cimetidine* (1g daily) for one week, plasma flecainide levels increased by about 30% and the half-life increased by about 10%.

Anti-smoking aids: Co-administration of *bupropion* with drugs that are metabolised 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 *bupropion* 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.

Cardiac glycosides: Flecainide can cause the plasma digoxin 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 digoxin plasma level in digitalized patients should be measured not less than six hours after any digoxin dose, before or after administration of flecainide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of flecainide in pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). 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 risk.

Lactation

Flecainide is excreted in human milk. Plasma concentrations obtained in a nursing infant are 5-10 times lower than therapeutic drug concentrations. 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.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000), not known (cannot be estimated from the available data).
Blood and lymphatic system disorders:
Uncommon: red blood cell count decreased, white blood cell count decreased and platelet count decreased
Immune system disorders:
Very rare: antinuclear antibody increased with and without systemic inflammation
Psychiatric disorders:
Rare: hallucination, depression, confusional state, anxiety, amnesia, insomnia
Nervous system disorders:
Very common: dizziness, which is usually transient
Rare: paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, - seizure, dyskinesia
Eye disorders:
Very common: visual impairment, such as diplopia and vision blurred
Very rare: corneal deposits
Ear and labyrinth disorders:
Rare: tinnitus, vertigo
Cardiac disorders:
Common: Proarrhythmia (most likely in patients with structural heart disease)
Frequency not known (cannot be estimated from the available data). Dose related increase in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4)
Uncommon: Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate
Frequency not known: atrioventricular block-second-degree and atrioventricular block third degree, cardiac arrest, bradycardia, cardiac failure/cardiac failure congestive, chest pain, hypotension, myocardial infarction, palpitations, sinus arrest, and tachycardia (AT or VT) or ventricular fibrillation . Demasking of a pre-existing Brugada syndrome.
Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea,
Rare: pneumonitis
Frequency not known: pulmonary fibrosis, insterstital lung disease

Gastrointestinal disorders:
Uncommon: nausea, vomiting, constipation, abdominal pain, increased appetite, diarrhea, dyspepsia, flatulence
Hepatobiliary disorders:
Rare: hepatic enzyme with or without jaundice
Frequency not known: hepatic dysfunction
Skin and subcutaneous tissue disorders:
Uncommon: dermatitis allergic, including rash, alopecia
Rare: serious urticaria
Very rare: photosensitivity reaction
Musculoskeletal and connective tissue disorders:
Not known: Arthralgia and Myalgia
General disorders and administration site conditions:
Common: asthenia, fatigue, pyrexia, oedema
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose with flecainide is a potentially life-threatening medical emergency. Increased drug susceptibility and plasma levels exceeding therapeutic levels may also result from drug interactions (see section 4.5). No specific antidote is known. There is no known way of rapidly removing flecainide from the system, but forced acid diuresis may theoretically be helpful. Neither dialysis nor haemoperfusion is helpful and injections of anticholinergics are not recommended.

Treatment should be supportive and may include removal of unabsorbed drug from the GI tract. Intravenous 8.4% sodium bicarbonate reduces flecainide activity. 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. balloon 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 diuresis with acidification of the urine theoretically promotes drug excretion. Intravenous fat emulsion and ECMO could be considered on a case-by-case basis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Class 1 anti-arrhythmic agent, -ATC code: C01BC04

Tambocor slows conduction through the heart, having his greatest effect on His Bundle conduction. It also acts selectively to increase anterograde and particularly retrograde accessory pathway refractoriness. Its actions may be reflected in the ECG by prolongation of the PR interval and widening of the QRS complex. The effect on the JT interval is insignificant.

5.2 Pharmacokinetic properties

Oral administration of flecainide results in extensive absorption, with bioavailability approaching 90 to 95%.

Flecainide does not appear to undergo significant hepatic first-pass metabolism. In patients, 200 to 500 mg flecainide daily produced plasma concentrations within the therapeutic range of 200- 1000 microg/L. Protein binding of flecainide is within the range 32 to 58%.

Recovery of unchanged flecainide in urine of healthy subjects was approximately 42% of a 20 0 mg oral dose, whilst the two major metabolites (Meta-O-Dealkylated and Dealkylated Lactam Metabolites) accounted for a further 14% each. The elimination half-life was 12 to 27 hours. The volume of distribution is 8.7 l/kg.

Intravenous administration of 0.5 – 2.0 mg/kg to healthy subjects resulted in plasma concentrations ranging from 70-340 mcg/l. Protein binding is low (about 40%). The volume of distribution is 8.7 l/kg.

The elimination half-life after IV administration to patients is 12 to 27 hours.

5.3 Preclinical safety data

In New Zealand white rabbits, high doses of flecainide produced some embryotoxic effects (increased resorption) and teratogenic effects (increased incidence of clubbed paws and skeletal abnormalities in sternebrae and vertebrae). Based on mg/kg body weight a safety margin of 8.7 for embryotoxic effects and 10.5 for teratogenic effects was calculated. These effects were not seen in Dutch belted rabbits or rats. The relevance of these findings to humans has not been established. Prolongation of gestation was seen in rats under a dose of 50mg/kg. No effects on fertility were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate
Glacial acetic acid
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Glass ampoules: 5 years

Diluted Product:
Chemical and physical in-use stability of the diluted solutions have been demonstrated for 24 hours at room temperature.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened ampoules: Do not store above 30°C. Do not freeze. Keep the ampoules in the outer carton.

For storage of the diluted products, see section 6.3.

6.5 Nature and contents of container

Boxes containing 5x15ml Type I clear glass ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Dilution: When necessary Tambocor injection should be diluted with, or injected into, sterile solution of 5% glucose. 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 500ml, otherwise a precipitate will form.

For single use only.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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