Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tambocor 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Flecainide Acetate 100 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from the UK:
White, round tablets, marked '3M' on one side and 'TR100' with a break-line on the other

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

'Tambocor' tablets are indicated for:

a) Symptomatic life threatening or disabling sustained ventricular tachycardia.
b) Premature ventricular contraction and/or non-sustained ventricular tachycardia which are causing disabling symptoms, where these are resistant to other therapy or when other treatment has not been tolerated.
c) 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 section 4.3, Contraindications).
d) Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways in the absence of left ventricular dysfunction (See section 4.3, Contraindications).
e) Paroxysmal atrial fibrillation and atrial flutter when treatment need has been established and in the absence of left ventricular dysfunction (See section 4.3, Contraindications).

Tambocor tablets can be used for the maintenance of normal rhythm following conversion by other means.

4.2 Posology and method of administration

Initiation of therapy should take place in the hospital environment with ECG monitoring.

Adults Only: The usual dose is 100mg twice daily initially with subsequent increments of 50mg every 4 days daily to the level of optimal response or a maximum dose of 400mg daily with subsequent reduction after 3-5 days to the lowest dose compatible with control. Some patients, particularly those with supra-ventricular, tachycardia will be adequately controlled on 50mg twice daily. Further reductions may be possible during long-term treatment.

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

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

Plasma levels: Based on PVC suppression, it appears that plasma levels of 200-1000 ng/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.

4.3 Contraindications

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.

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

Use with other Class 1 anti-arrhythmics.

4.4 Special warnings and precautions for use

Electrolyte disturbances should be corrected before using Tambocor, and should be checked during therapy particularly if diuretics are being administered.

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.

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

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 pre-existing 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 non-life-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.

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 sodium channel blockers is not recommended.
Anti-depressants; *fluoxetine* 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*, *lopinavir* and *indinavir* (increased risk of ventricular arrhythmias (avoid concomitant use).

Diuretics: Class effect due to hypokalaemia giving rise to cardiac toxicity.

Ulcer healing drugs: *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.

Treatment with Tambocor is compatible with use of oral anti-coagulants.

4.6 Fertility, pregnancy and lactation

There is no evidence as to drug safety in human pregnancy. Use should be avoided during pregnancy or lactation unless considered essential by the physician.

In New Zealand White rabbits high doses of flecainide caused some foetal abnormalities, but these effects were not seen in Dutch Belted rabbits or rats. 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 is excreted in human milk and appears in concentrations which reflect those in maternal blood. The risk of adverse effects to the nursing infant is very small.

4.7 Effects on ability to drive and use machines

No effect.

4.8 Undesirable effects

Body as a Whole: Asthenia, fatigue, fever, oedema.
Cardiovascular: Pro-arrhythmic effects occur but are most likely in patients with structural heart disease and/or significant left ventricular impairment.

In patients with atrial flutter the use of Tambocor has been associated with 1:1 AV conduction following initial atrial slowing with resultant ventricular acceleration. This has been seen most commonly following the use of the injection for acute conversion. This effect is usually short lived and abates quickly following cessation of therapy.

The following adverse effects have also been reported: AV block-second-degree and third degree, bradycardia, cardiac failure/congestive cardiac failure, chest pain, hypotension, myocardial infarction, palpitation and sinus pause or arrest and tachycardia (AT or VT).

Ventricular arrhythmics may be exacerbated and occasionally non-resuscitable ventricular fibrillation may occur.

Skin and Appendages: A range of allergic skin reactions have been reported including rashes and alopecia. There have also been isolated cases of photosensitivity.

Gastrointestinal: Occasionally nausea and vomiting. The following have also been reported: abdominal pain, anorexia, constipation, diarrhoea, dyspepsia and flatulence (bloating).

Liver and Bilary System: A number of cases of elevated liver enzymes and jaundice have been reported in association with Tambocor treatment. Hepatic dysfunction, colestasis and hepatic failure have been reported.

Neurological: Most commonly giddiness, dizziness and lightheadedness and headache may occur and are usually dose related. During long term therapy a few cases of peripheral neuopathy, paraesthesia and ataxia have been reported. There also have been reports of flushing, headache, hypoaesthesia, increased sweating, somnolence, syncope, tinnitus, tremor and vertigo.

Ophthalmological: Visual disturbances, such as double vision and blurring of vision may occur. Extremely rare cases of corneal deposits have also been reported.

Haematological: Blood dyscrasias have also been reported.

Respiratory: Dyspnoea and rare cases of pneumonitis have been reported.

Psychiatric: Depression, anxiety and insomnia have been reported.

4.9 Overdose

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 may include therapy with an inotropic agent, intravenous calcium, giving circulatory assistance (e.g. balloon pumping), mechanically assisting respiration, or temporarily inserting a transvenous pacemaker if there are severe conduction disturbances or the patient's left ventricular function is otherwise compromised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tambocor is a potent sodium channel blocking agent.

Tambocor slows conduction through the heart. 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 600 mg flecainide daily produced plasma concentrations within the therapeutic range of 200-1000 µg/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 200mg 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.

5.3 Preclinical safety data

No information given.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch
Croscarmellose sodium
Microcrystalline cellulose (E460i)
Hydrogenated vegetable oil
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Keep the tablets in the outer container to protect from light.

6.5 Nature and contents of container

Over-labelled cardboard carton containing two aluminum blister strips (30 tablets per blister)

Pack size: 60 tablets.

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

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1659/035/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT