SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tambocor 10mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 15 ml of a solution of flecainide acetate 10 mg/ml.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Serious sustained life threatening ventricular arrhthymias that have not respoded to other drugs.

4.2 Posology and method of administration

In an emergency or for rapid effect, or as a slow intravenous infusion when prolonged administration is required.

a) Bolus injection: Administer 2 mg/kg over not less than ten minutes, or in divided doses. Alternatively dilute with 5% dextrose and give as a mini-infusion.

Continuous ECG monitoring is recommended. Stop the injection when the arrhythmia is controlled.

For sustained ventricular tachycardia, or people with a history of cardiac failure (who may become decompensated during administration) give the initial dose over 30 minutes and monitor the ECG carefully.

The maximum recommended bolus dose is 150 mg.

b) Intravenous infusion: The recommended procedure is to start with a slow injection of 2 mg/kg over 30 minutes, then continue 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.

The maximum recommended infusion duration is 24 hours; if exceeded, and in patients receiving high doses, monitor plasma levels.

The maximum cumulative dose over the first 24 hours should not exceed 600 mg.

In severe renal impairment (creatinine clearance < 35 ml/min/1.73 sq.m.) reduce the above dosage recommendations by half.

Oral maintenance dosing should be started as soon as possible after stopping the infusion.

Children: Tambocor is not recommended in children under 12, 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.

4.3 Contraindications

Hypersensitivity to flecainide or to any of the excipients.

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

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.

Known Brugada syndrome.

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.

4.4 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 disturbances) .

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.

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.

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

Tambocor, 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 4.8).

Tambocor should be used with caution in patients with impaired renal function (creatinine clearance $\leq$ 35 ml/min/1.73 m2) 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.

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.

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.

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

For further warnings and precautions please refer to section 4.5 (Interaction).

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 antiarrhythmic drugs where additive effects may occur or where drugs interfere with the metabolism of flecainide.
Flecainide should not be administered concomitantly with other class I antiarrythmics. The following known categories of drugs may intereact 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 betablockers, 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, paroxetine* and other antidepressants increases plasma flecainide concentration; increased risk of arrhythmias with *tricyclics*; manufacturer of *reboxetine* advises caution.

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).

An increase of plasma levels may also result from renal impairment due to a reduced clearance of flecainide

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-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*, *lopinavar* and *indinavir* (increased risk of ventricular arrhythmias) avoid concomitant use

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

H2 antihistamines (for the treatment of gastric ulcers): *cimetidine* inhibits 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 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 *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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy information

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 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.

Lactation information

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.

4.7 Effects on ability to drive and use machines
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)

4.8 Undesirable effects
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/l0), 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, convulsion, 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 and/or significant left ventricular impairment).
Frequency not known (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).

Uncommon: Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate.

Frequency not known (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.

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea
Rare: pneumonitis
Frequency not known (cannot be estimated from the available data): pulmonary fibrosis, interstitial lung disease

Gastrointestinal disorders:
Uncommon: nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence

Hepatobiliary disorders:
Rare: hepatic enzymes increased with and without jaundice
Frequency not known (cannot be estimated from the available data): hepatic dysfunction

Skin and subcutaneous tissue disorders:
Uncommon: dermatitis allergic, including rash, alopecia
Rare: serious urticaria
Very rare: photosensitivity reaction

General disorders and administration site conditions:
Common: asthenia, fatigue, pyrexia, oedema

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

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.

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 diuresis with acidification of the urine theoretically promotes drug excretion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Tambocor is a Class 1 anti-arrhythmic (local anaesthetic) agent. ATC code: C01BC04.

Tambocor slows conduction through the heart, having its greatest effect on His Bundle conduction. It also acts selectively to increase anterograde and particularlyretrograde 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
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 was 7 to 19 hours.

5.3 Preclinical safety data
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Acetate

Glacial Acetic Acid

Water for injections

6.2 Incompatibilities
None known

6.3 Shelf life
3 year

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze. Protect from light.

6.5 Nature and contents of container
Boxes containing 5 x 15 ml glass ampoules.

6.6 Special precautions for disposal and other handling
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.

7. MANUFACTURER

Cenexi, Fontenay-sous-Bois, France for Meda Pharma GmbH & CO.KG, Bad Homburg, Germany

8. MARKETING AUTHORISATION HOLDER

Megapharm Ltd,
P.O.B 519 Hod Hasharon 4510501
Israel

The format of this leaflet was determined by the ministry of health and its content was checked and approved in June 2015.