

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

**Tambocor 50mg, 100mg Tablets**

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Flecainide Acetate 50mg, 100mg

### 3. PHARMACEUTICAL FORM

Tablets

#### 4.1 Therapeutic indications

Tambocor Tablets 50mg:

- a) Serious sustained life threatening supraventricular arrhythmias that have not responded to other drugs.
- b) Paroxysmal atrial fibrillation and atrial flutter.

Tambocor Tablets 100mg:

- a) Serious sustained life threatening ventricular arrhythmias that have not responded to other drugs.
- b) Paroxysmal atrial flutter.

Tambocor tablets are for oral administration.

#### 4.2 Posology and method of administration

Adults: Supraventricular arrhythmias: The recommended starting dosage is 50mg twice daily and most patients will be controlled at this dose. If required the dose may be increased to a maximum of 300mg daily.

Ventricular arrhythmias: The recommended starting dosage is 100mg twice daily. The maximum daily dose is 400mg and this is normally reserved for patients of large build or where rapid control of the arrhythmia is required.

After 3-5 days it is recommended that the dosage be progressively adjusted to the lowest level which maintains control of the arrhythmia. It may be possible to reduce dosage during long-term treatment.

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.

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 700-1000 ng/ml are associated with increased likelihood of adverse experiences.

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

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

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

Treatment with oral Tambocor should be under direct hospital or specialist supervision for patients with:

- a) AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways
- b) Paroxysmal atrial fibrillation in patients with disabling symptoms.

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

Tambocor 100 mg can be divided, in order to administer 50 mg dose.

### **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.

Tambocor 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 nonprogrammable 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 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 Tambocor 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 antiarrhythmics. 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 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 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.

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

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. 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

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 tablets have 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  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

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.

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.it/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.it>.

## 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. 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. 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

## 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 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 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**

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**

Pregelatinised maize Starch  
Croscarmellose Sodium  
Microcrystalline Cellulose  
Hydrogenated Vegetable Oil  
Magnesium Stearate

## **6.2 Incompatibilities**

None known

## **6.3 Shelf life**

5 years

## **6.4 Special precautions for storage**

Do not store above 25°C. Keep tablets in the outer carton in order to protect from light and moisture.

## **6.5 Nature and contents of container**

UPVC/PVDC blister packs containing 60 tablets

## **6.6 Special precautions for disposal**

Not applicable

# **7 MANUFACTURER**

3M Health care Ltd., Loughborough, UK for Meda Pharma GmbH & CO.KG, Bad Homburg, Germany

# **8 MARKETING AUTHORISATION HOLDER**

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