SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tambocor 50 mg tablets
Tambocor 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tambocor 50 mg tablets: Each tablet contains Flecainide acetate 50 mg.
Tambocor 100 mg tablets: Each tablet contains Flecainide acetate 100 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Tambocor 50 mg tablets: White, circular, biconvex tablets.

Tambocor 100 mg tablets: White, circular, biconvex tablets with a break-line. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tambocor 50 mg Tablets:
a) Serious sustained life threatening supraventricular arrhythmias that have not responded to other drugs.
b) Paroxysmal atrial fibrillation and atrial flutter.

Tambocor 100 mg Tablets:
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 50 mg twice daily and most patients will be controlled at this dose. If required the dose may be increased to a maximum of 300 mg daily.

Ventricular arrhythmias:
The recommended starting dosage is 100 mg twice daily. The maximum daily dose is 400 mg 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 tablets 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 premature ventricular contraction (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 100 mg daily (or 50 mg 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 tablets can be divided, in order to administer 50 mg dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Tambocor tablets is contraindicated in cardiac failure and in patients with a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.

Further contraindications include reduced or impaired ventricular function, cardiogenic shock, severe bradycardia, severe hypotension and concomitant use with disopyramide.

It is also contraindicated 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 tablets 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

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

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

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

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

Tambocor tablets, 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).

Tambocor tablets should be avoided in patients with structural heart disease or abnormal left ventricular function (see section 4.8).

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

Flecainide has a selective effect that increases the refractory period of the anterograde, and especially, the retrograde pathways. Flecainide acetate prolongs the QT interval and widens the QRS complex by 12-20%. The effect on the JT interval is insignificant. Nevertheless, there have been reports of prolongation of the JT interval of up to 4%. This action is less marked than that observed with the class 1a antiarrhythmic drugs however.

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

Since flecainide acetate elimination from the plasma can be markedly slower in patients with significant hepatic impairment, Tambocor tablets 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 tablets should be used with caution in patients with impaired renal function (creatinine clearance ≤ 35 ml/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 acetate elimination from plasma may be reduced in the elderly. This should be taken into consideration when making dose adjustments.

Tambocor tablets is not recommended in children under 12 years of age, as there is insufficient evidence of its use in this age group (see section 4.2)

Electrolyte disturbances (e.g. hypo- and hyperkalaemia) should be corrected before using Tambocor tablets (see section 4.5 for some drugs causing electrolyte disturbances).

Severe bradycardia or pronounced hypotension should be corrected before using Tambocor tablets.

Flecainide acetate 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 tablets 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.

Tambocor tablets should be used with caution in patients with "sick sinus syndrome".

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 flecainide acetate.

The minor negative inotropic effect of flecainide acetate 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.

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

In a large scale, placebo-controlled clinical trial; in post-myocardial infarction patients with asymptomatic ventricular arrhythmia, oral flecainide acetate 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 acetate-treated patients with more than one myocardial infarction. Comparable placebo-controlled clinical trials have not been done to determine if flecainide acetate 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 acetate in children and infants. Flecainide acetate is not approved for use in children below the age of 12 years, however flecainide acetate toxicity has been reported during treatment with flecainide acetate 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

For further warnings and precautions please refer to section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

Class I anti-arrhythmics: Tambocor tablets should not be administered concomitantly with other class I antiarrythmics. Concomitant use of quinidine can decrease flecainide acetate clearance by 23%.

Class II anti-arrhythmics: the possibility of additive negative inotropic effects of class II anti-arrhythmics i.e. beta-blockers, and other cardiac depressants with Tambocor tablets should be recognised.

Class III anti-arrhythmics: if Tambocor tablets is given in the presence of *amiodarone*, the usual Tambocor tablets 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: the use of Tambocor tablets with 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). 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 Tambocor tablets. Hypokalaemia may result from the concomitant use of diuretics, corticosteroids or laxatives.

Antivirals: plasma concentrations are increased by ritonavir and fixed-combination products containing ritonavir (increased risk of ventricular arrhythmias, avoid concomitant use).

Anti-malarials: quinine increases plasma concentration of flecainide.

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

Anti-depressants: fluoxetine, paroxetine and other antidepressants increase 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.

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

Diuretics: Class effect due to hypokalaemia giving rise to cardiaotoxicity.

H_2 antihistamines (for the treatment of gastric ulcers): The H_2 antagonist cimetidine inhibits metabolism of flecainide. In healthy subjects receiving cimetidine (1g daily) for one week, the AUC of flecainide increased by about 30% and the half-life increased by about 10%.

Anti-smoking aids: Co-administration of bupropion (metabolised by CYP2D6) with Tambocor tablets 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 Tambocor tablets, the need to decrease the dose of the original medication should be considered.

Cardiac glycosides: Flecainide acetate can cause the plasma digoxin level to rise by about 15%, which is unlikely to be of clinical significance for patients with plasma levels within 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 Tambocor tablets.

Anticoagulants: The treatment with Tambocor tablets is compatible with the 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, in animal studies high doses of flecainide acetate caused some foetal abnormalities, but these effects were not seen in Dutch Belted rabbits or rats (see section 5.3). The relevance of these findings to humans has not been established. Data have shown that flecainide acetate crosses the placenta to the foetus in patients taking flecainide acetate during pregnancy.

Tambocor tablets should only be used in pregnancy if the benefit outweighs the risks. If Tambocor tablets is used maternal plasma should be monitored throughout pregnancy.

Breast-feeding
Flecainide acetate is excreted in human milk and appears in concentrations which reflect those in maternal blood. Plasma concentrations obtained in a nursing infant are 5-10 times lower than therapeutic drug concentrations (see section 5.2). Although the risk of adverse effects to the nursing infant is very small, Tambocor tablets should only be used during breast-feeding if the benefit outweighs the risks.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness and visual disturbances have been reported. These effects are usually transient. However, if these undesirable effects are experienced then driving ability, operation of machinery and work without a secure fit may be affected.

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 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000) 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. These changes are usually mild.

Immune system disorders:
Very rare: antinuclear antibody increased with and without systemic inflammation

Psychiatric disorders:
Rare: hallucination, depression, confusional state, anxiety, amnesia, insomnia, nervousness

Nervous system disorders:
Very common: giddiness, dizziness and light headedness which are usually transient
Rare: During long term therapy a few cases of neuropathy peripheral, paraesthesia and ataxia have been reported. Rare instances of dyskinesia have been reported, which have improved on withdrawal of flecainide acetate therapy. Hypoaesthesia, hyperhidrosis, syncope, tremor, somnolence, headache and convulsion.

Eye disorders:
Very common: visual impairment, such as diplopia and vision blurred. These are usually transient and disappear upon continuing or reducing the dosage.
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).
Uncommon: Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate. These effects are most common following the use of the injection for acute conversion. This effect is usually short lived and abates quickly following cessation of therapy.
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 pause or arrest and tachycardia (AT or VT) or ventricular fibrillation. Demasking of a pre-existing Brugada syndrome. Dose-related increases in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4).

Vascular disorders
Rare: flushing

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea

Rare: pneumonitis
Not known: pulmonary fibrosis, interstitial lung disease

Gastrointestinal disorders:
Uncommon: nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence
Very rare: dry mouth, taste disorders

Hepatobiliary disorders:
Rare: hepatic enzymes increased with and without jaundice. So far this has always been reversible on stopping treatment.
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
Very rare: arthralgia and myalgia

Reproductive system and breast disorders
Very rare: impotence

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Overdosage with flecainide acetate is a potentially life threatening medical emergency. Increased drug susceptibility and plasma levels exceeding therapeutic levels may also result from drug interaction (see section 4.5). No specific antidote is known. There is no known way to rapidly remove flecainide acetate from the system. Neither dialysis nor haemoperfusion is effective.

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 circulatory assistance (e.g. balloon pumping) and mechanical ventilation. 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: Cardiac therapy. Antiarrhythmic Class Ic. ATC code: C01BC04.

Flecainide acetate is a class 1c antiarrhythmic agent with negative inotropic activity. It binds to the sodium channels of muscle membranes, producing a potent slowing of cardiac impulse conduction and a suppression of spontaneous premature ventricular complexes.
Within the heart flecainide acetate binds strongly to fast sodium channels and so slows the rate of depolarisation and conduction in the atria, atrio-ventricular node, ventricular and Purkinje fibres is decreased. The most profound effect is observed upon the Purkinje fibres. 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

Following oral administration, the absorption of flecainide acetate is almost complete (90%), and peak plasma concentration occurs after 3-4 hours. It is weakly plasma bound (40%). 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%. Oral absorption does not appear to be affected by either food or antacids.

In healthy subjects the plasma half-life of flecainide acetate is 12-13 hours after a single oral dose. However, the plasma half-life is prolonged after multiple oral doses (16 hours) and in patients with ventricular arrhythmia's (20 hours).

After oral absorption flecainide acetate is metabolised by the liver and undergoes extensive biotransformation. Approximately 86% of a dose is excreted in the urine, 27% as unchanged flecainide acetate and 59% as metabolites. The two major urinary metabolites are meta-O-dealkylated flecainide acetate and meta-O-dealkylated lactam of flecainide acetate. (Only 5% of an oral dose is excreted in the faeces). These metabolites have no clinically significant antiarrhythmic effects.

The rate of flecainide acetate elimination from plasma is reduced in the presence of renal failure, liver disease and congestive heart failure. The urinary excretion of flecainide acetate is reduced in patients with renal failure and significantly so in patients with severe renal failure.

5.3 Preclinical safety data

Flecainide acetate has not shown any significant systemic target organ toxicity in repeat dose studies in animals. It was neither mutagenic nor carcinogenic in rats and mice.
Flecainide acetate can cross the placenta and is excreted in breast milk. It has shown fetotoxicity at high doses in rats and caused foetal abnormalities at high dosage in New Zealand white rabbits but not in Dutch Belted rabbits or rats. The relevance of these findings to humans has not yet been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch
Microcrystalline cellulose
Croscarmellose sodium
Hydrogenated vegetable oil
Magnesium stearate

6.2 Incompatibilities
None known

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container
Blister. Approved package size: 60 tablets.

6.6 Special precautions for disposal
Not applicable

7. MARKETING AUTHORISATION HOLDER
Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER(S)
Tambocor 50 mg tablets: 111-73-29433
Tambocor 100 mg tablets: 123-99-23293

Revised in December 2024 according to MOH guidelines.