SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TAMBOCOR CR 50, flecainide acetate 50 mg per capsule.

TAMBOCOR CR 100 flecainide acetate 100 mg per capsule.

TAMBOCOR CR 150 flecainide acetate 150 mg per capsule.

TAMBOCOR CR 200 flecainide acetate 200 mg per capsule.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TAMBOCOR CR 50: Each controlled release capsule contains flecainide acetate 50 mg.

TAMBOCOR CR 100: Each controlled release capsule contains flecainide acetate 100 mg.

TAMBOCOR CR 150: Each controlled release capsule contains flecainide acetate 150 mg.

TAMBOCOR CR 200: Each controlled release capsule contains flecainide acetate 200 mg.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules

TAMBOCOR CR 50: Hard, white to off white beadlets in size 4 hard gelatin capsule with a white opaque cap and a white opaque body.

TAMBOCOR CR 100: Hard, white to off-white beadlets in size 3 hard gelatin capsule with a light grey cap and an opaque white body, printed TR on the cap and 100 on the body, in black.

TAMBOCOR CR 150: Hard, white to off white beadlets in size 2 hard gelatin capsule with a opaque grey cap and an opaque grey body.

TAMBOCOR CR 200: Hard, white to off-white beadlets in size 1 hard gelatin capsule with a light grey cap and an opaque pink body, printed TR on the cap and 200 on the body, in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment with TAMBOCOR CR should be initiated in a hospital for control of the following dysrhythmias:

- Sustained ventricular tachydysrhythmias.
- AV nodal reciprocating tachycardia; Wolff-Parkinson-White Syndrome and similar conditions with accessory pathway and anterograde or retrograde conduction.
- Paroxysmal atrial fibrillation in patients with disabling symptoms. Dysrhythmias of recent onset will respond more readily.

In addition, TAMBOCOR CR is indicated in premature ventricular contractions and/or non-sustained ventricular tachycardia which are causing disabling symptoms

TAMBOCOR CR can be used for the maintenance of normal rhythm following conversion by other means.

4.2 Posology and method of administration

Posology

Adults:

The controlled-release form of TAMBOCOR CR is administrated as a once-daily dose.

1. Documented supraventricular tachycardia:

   The recommended starting dosage is 100 mg per day.

   An increase of the dosage should only be considered only after a period of 4 to 5 days.

   The optimal dosage is 200 mg per day.

   The maximum dosage is 300 mg per day.

2. Documented ventricular tachycardia:

   The usual dosage is 200 mg per day.

   An increase of the dosage should only be considered after a period of 4 to 5 days.

   The maximum dosage is 300 mg per day.

3. High-risk patients:

   [e.g. elderly, history or symptoms suggestive of heart failure, severe renal insufficiency (creatinine clearance less than or equal to 30 ml/min/m²)]

The initial dose must not exceed 100 mg per 24 hours: it ranges from 50 to 100 mg/24 hours depending on the patient's state.

The dosage can be increased or decreased by steps of 50 mg per day, bearing in mind that a minimum period of 4 to 5 days is necessary to establish new steady-state plasma levels after each modification. Patients should be monitored by clinical examination and by electrocardiogram.

Note: If a patient is changed over from TAMBOCOR TABLETS to TAMBOCOR CR, the dosage should be based on the total daily dose (e.g. 2 x 100 mg TAMBOCOR TABLETS to TAMBOCOR CR 200).

Method of administration

Oral.

4.3 Contraindications

TAMBOCOR CR must never be used in:

- Patients who are hypersensitive to flecainide acetate or any of the excipients of TAMBOCOR CR (see section 6.1).
- Myocardial infarction (old or acute).
- Heart failure, regardless of the type of dysrhythmia.
- Complete left bundle branch block, bifascicular block, 2nd and 3rd degree atrioventricular block, sinus node dysfunction and atrial disease, in the absence of pacing.
- Patients with long standing atrial fibrillation and haemodynamically significant valvular heart disease.

TAMBOCOR CR is generally not recommended in combination with class I anti-dysrhythmics.

4.4 Special warnings and precautions for use

TAMBOCOR CR was tested in a multicentre randomised double-blind trial (CAST trial) in patients with asymptomatic, non-life-threatening ventricular dysrhythmia with a history of myocardial infarction more than 6 days and less than 2 years before inclusion. The incidence of mortality and nonfatal

cardiac arrests was higher with flecainide than in the placebo control group.

No controlled trial has demonstrated a beneficial effect of TAMBOCOR CR in terms of survival or sudden death.

Pro-dysrhythmic effects:

TAMBOCOR CR can induce a more severe form of dysrhythmia, increase the frequency of a pre-existing dysrhythmia or worsen the severity of symptoms.

Spontaneous variations of the dysrhythmia specific to the patient may be difficult to distinguish from deterioration induced by administration of a medicinal product. Treatment should be stopped in the case of more numerous or polymorphous ventricular premature complexes.

History of heart failure:

Because of its negative inotropic action, TAMBOCOR CR must be prescribed under strict surveillance of cardiac function in patients with a history or symptoms suggestive of heart 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 CR has been shown to increase mortality risk of post-myocardial infarction patients with asymptomatic ventricular arrhythmia.

Electrocardiographic changes:

TAMBOCOR CR must be administered cautiously in patients with pre-existing conduction disorders. It should be stopped if atrioventricular block, permanent complete branch block or sinoatrial block occur during treatment. The dosage should be decreased in the case of widening of QRS complexes by more than 25 % of baseline values.

In the case of modification of the dosage of TAMBOCOR CR or concomitant treatment able to affect cardiac conduction, patients, especially those with pre-existing conduction disorders, should be

closely monitored by electrocardiogram.

TAMBOCOR CR 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 CR 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 CR.

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

Electrolyte disorders:

Hypokalaemia, hyperkalaemia or hypomagnesaemia can potentiate the pro-dysrhythmic effects of class I anti-dysrhythmic and must therefore be corrected before administration of TAMBOCOR CR.

Renal insufficiency

In patients with renal insufficiency (creatinine clearance ≤ 35 ml/min/1,73 m^2), the rate of elimination of TAMBOCOR CR can be decreased, resulting in a risk of plasma and tissue accumulation of the medicinal product which can be responsible for adverse effects. Therapeutic medicine monitoring is recommended, and this risk justifies dosage adjustment.

Elderly patients:

The rate of flecainide elimination from plasma may be reduced in elderly people and doses may need to be adjusted accordingly. The occurrence of cardiac arrest and symptomatic conduction

disturbances is higher in the elderly.

Hepatic impairment:

Since TAMBOCOR CR elimination from the plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR CR should not be used in such patients. Plasma level monitoring is strongly recommended in these circumstances.

General

Severe bradycardia or pronounced hypotension should be corrected before using TAMBOCOR CR.

TAMBOCOR CR should be avoided in patients with structural organic heart disease or abnormal left ventricular function.

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

Flecainide as contained in TAMBOCOR CR, is a narrow therapeutic index medicine. It requires caution and close monitoring when switching a patient to a different formulation.

Paediatric population

TAMBOCOR CR is not recommended in children under 18 years of age, as there is insufficient evidence of its use in this age group.

4.5 Interaction with other medicines and other forms of interaction

Class I anti-dysrhythmics: TAMBOCOR CR must not be co-prescribed with other class I anti-dysrhythmics, apart from exceptional cases, because of the increased risk of adverse cardiac effects (automatism, conduction, prodysrhythmic effects, inotropism).

Other classes of anti-dysrhythmics: combination with anti-dysrhythmics of other classes is only exceptionally indicated and is usually very delicate, requiring close clinical and ECG monitoring.

Class II anti-dysrhythmics: the possibility of additive negative inotropic effects of betablockers and other cardiac depressants with TAMBOCOR CR should be recognised.

Class III anti-dysrhythmics: when flecainide is given in the presence of amiodarone, the usual TAMBOCOR CR 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-dysrhythmics: use of TAMBOCOR CR with other sodium channel blockers is not recommended.

Combination with medicinal products possessing negative inotropic or bradycardic properties and/or slowing atrioventricular conduction or intraventricular conduction (beta-blockers, amiodarone, digitalis glycosides, verapamil and diltiazem, tricyclic antidepressants, local anaesthetics) requires close clinical and ECG surveillance, particularly in the elderly and at the beginning of treatment.

Cardiac glycosides: TAMBOCOR CR 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 TAMBOCOR CR.

H2 antihistamines (for the treatment of gastric ulcers): Cimetidine inhibits metabolism of TAMBOCOR CR. In healthy subjects receiving cimetidine (1 g daily) for one week, plasma flecainide levels increased by about 30 % and the half-life increased by about 10 %. Reduction of TAMBOCOR CR dosage of up to 50 % advisable.

Life-threatening or even lethal adverse events due to interactions causing increased plasma concentrations may occur (see section 4.9). TAMBOCOR CR is metabolised by CYP2D6 to a large extent, and concurrent use of medicine 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 TAMBOCOR CR, respectively (see below).

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

Hypokalaemia, but also hyperkalaemia or other electrolyte disturbances should be corrected before administration of TAMBOCOR CR. Hypokalaemia may result from the concomitant use of diuretics, corticosteroids or laxatives.

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 TAMBOCOR CR 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 TAMBOCOR CR.

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.

Anti-smoking aids: Co-administration of bupropion with medicine that are metabolised by CYP2D6 isoenzyme including TAMBOCOR CR, 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 CR, the need to decrease the dose of the original medication should be considered.

Anticoagulants: Treatment with TAMBOCOR CR is compatible with use of oral anticoagulants

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. It should not be administrated in the case of suspected pregnancy or during the first three months of pregnancy.

Breastfeeding

Safety in breastfeeding has not been established.

4.7 Effects on ability to drive and use machines

TAMBOCOR CR has no or negligible influence on the ability to drive and use machines. However, driving ability, operation of machinery and working without a secure fit may be affected by adverse reactions such as dizziness and visual disturbances (if present).

4.8 Undesirable effects

The following side effects have been observed during treatment with TAMBOCOR CR with following frequencies: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Nervous system disorders

Very common: Dizziness, and light-headedness which are usually transient have been reported.

Rare: Paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, convulsion, dyskinesia.

Eye disorders

Very common: Visual impairment and disturbances, such as double vision and blurring of vision may occur.

Very rare: Corneal deposits.

Cardiac disorders

Common: Pro-dysrhythmic effects may occur in any patient but very common 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.

Frequency not known: Dose-related increases in PR and QRS intervals may occur (see section 4.4).

Altered pacing threshold (see section 4.4).

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: Pulmonary fibrosis, interstitial lungs disease.

Gastrointestinal disorders

Uncommon: Nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence.

Hepato-biliary disorders

Rare: Elevated liver enzymes 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

Frequency 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage with TAMBOCOR CR is a potentially life-threatening medical emergency. Increased medicine susceptibility and plasma levels exceeding therapeutic levels may also result from medicine interaction (see section 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.

Overdose with TAMBOCOR CR requires surveillance in hospital in a specialised unit. It is marked by electrocardiographic changes, particularly widening of the QRS complex, and development of cardiogenic shock. Treatment is essentially symptomatic.

It can be accompanied by neurosensory, neuropsychiatric and cardiac symptoms.

Treatment should be supportive and may include removal of unabsorbed medicine 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 medicine excretion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Class 1 anti-arrhythmic (local anaesthetic) agent. ATC code: C01BC04.

A 6.2 Cardiac medicines (depressants) - (Class I anti-dysrhythmic)

Flecainide acetate is a class I anti-dysrhythmic (local anaesthetic) agent. Flecainide acetate possesses a negative inotropic effect.

Flecainide acetate:

- prolongs intra-atrial, nodal and intraventricular conduction times,
- slightly increases atrial and ventricular effective refractory periods,
- increases the effective refractory period of the atrioventricular node,
- increases the refractory period of retrograde and anterograde accessory pathways,
- does not induce any significant modifications of heart rate except in patients with sinus node dysfunction.

There is a marked linear relationship between plasma flecainide acetate concentrations and widening of the QRS complex, a marker of the anti-dysrhythmic effect.

5.2 Pharmacokinetic properties

TAMBOCOR CR capsules contain polymer-coated microgranules, allowing controlled release of flecainide acetate. Each microgranule constitutes a controlled release form of flecainide acetate, allowing prolongation of the absorption time without modifying the elimination parameters.

Absorption of flecainide acetate via the oral route is greater than 80 % of the dose administered. After administration of one flecainide acetate capsule, plasma flecainide concentrations gradually increase

after a lag time of 2 to 3 hours to reach a peak between the 21st and 25th hour and remain at plateau levels until after the 30th hour. Plasma concentrations are proportional to the dose between 50 mg and 300 mg. This dose relation is maintained at steady-state for doses of 100 to 300 mg.

Absorption of flecainide acetate from capsule is not modified by food.

Steady-state is reached after five days of treatment with minimal fluctuations, and 50 % flattening of plasma concentration peaks compared to the tablet form.

Flecainide acetate is widely and rapidly distributed in the tissues.

The mean volume of distribution is 8,31 L/kg.

Protein binding is low (about 40 %).

Flecainide acetate is essentially eliminated in the urine:

25 % of the dose is eliminated after 24 hours in the unchanged form. Haemodialysis does not appear to be an effective way to eliminate flecainide acetate. Flecainide acetate is also eliminated by metabolism, especially via the cytochrome 2D6 pathway.

The apparent plasma elimination half-life is about 12 to 14 hours; it is not modified with the flecainide acetate capsule form.

No enzyme induction or inhibition phenomena have been observed after prolonged dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients

Microcrystalline cellulose

Methacrylic acid – methyl methacrylate copolymer (1:2)

Polyethylene glycol 400 (Macrogol 400)

Talc

Capsule shell

Gelatin

Titanium dioxide (E171)

Iron oxide black (E172)

Erythrosine

Printing ink

Shellac

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C.

Protect from light.

Keep blisters in the carton until required for use.

6.5 Nature and contents of container

Blister packs of 15, 30 and 60 capsules.

Blisters are made of clear UPVC / PVDC with aluminium foil backing.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iNova Pharmaceuticals (Pty) Limited

15 E Riley Road

Bedfordview

South Africa

8 REGISTRATION NUMBER

TAMBOCOR CR 50: 37/6.2/0198

TAMBOCOR CR 100:37/6.2/0199

TAMBOCOR CR 150:37/6.2/0200

TAMBOCOR CR 200:37/6.2/0201

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

TAMBOCOR CR: 2 March 2012

10 DATE OF REVISION OF THE TEXT

05 September 2021