NEW ZEALAND DATA SHEET
TAMBOCOR™ Tablets
TAMBOCOR™ CR Capsules

1 PRODUCT NAME
TAMBOCOR 50 mg tablets

TAMBOCOR 100 mg tablets*

TAMBOCOR CR 100 mg capsules

TAMBOCOR CR 200 mg capsules

TAMBOCOR CR 300 mg capsules*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each TAMBOCOR 50 mg tablet contains flecainide acetate 50 mg.

Each TAMBOCOR 100 mg tablet contains flecainide acetate 100 mg.

Each TAMBOCOR CR 100 mg capsule contains flecainide acetate 100 mg.

Each TAMBOCOR CR 200 mg capsule contains flecainide acetate 200 mg.

Each TAMBOCOR CR 300 mg capsule contains flecainide acetate 300 mg.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Tablet

TAMBOCOR 50 mg tablet: White, circular, biconvex tablets 6.5 mm in diameter marked TR50 on one face and plain on the other face.

TAMBOCOR 100 mg tablets: White, circular, biconvex tablets 8.5 mm in diameter marked TR100 on one face over a break line and plain on the other face.

Modified release capsule

TAMBOCOR CR 100 mg capsule: Grey and white hard gelatin capsules with the captions 3M and 100 printed in black ink in the axial direction on the respective capsule halves.

TAMBOCOR CR 200 mg capsule: Grey and pink hard gelatin capsules with the captions 3M and 200 printed in black ink in the axial direction on the respective capsule halves.

TAMBOR CR 300 mg capsule: Grey and light blue with the captions 3M and 300 printed in black ink in the axial direction on the respective capsule halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In patients without structural heart disease and without myocardial infarction tablets and capsules are indicated for the prevention of:

Supraventricular arrhythmias

- paroxysmal supraventricular tachycardias (PSVT) including atrioventricular nodal re-entrant tachycardia, atrioventricular re-entrant tachycardia and other supraventricular tachycardias of unspecified mechanism associated with disabling symptoms;
- paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms.

Ventricular arrhythmias

- Documented life-threatening ventricular arrhythmias such as sustained ventricular tachycardia (VT) if they are considered life-threatening in the judgement of the attending physician. Not indicated for less severe ventricular arrhythmias even if symptomatic.

Use of TAMBOCOR in chronic atrial fibrillation has not been adequately studied and is not recommended.

4.2 Dose and method of administration

TAMBOCOR tablets and TAMBOCOR CR capsules are for oral administration.

The following regimen is suggested as a guideline. However, dosage may need to be modified as dictated by the weight, age or clinical status of the patient.

General considerations

- Prior to treatment perform an adequate clinical assessment of the patient to establish that there is no structural heart disease or left ventricular systolic dysfunction.
- TAMBOCOR can increase pacing or defibrillation thresholds, so this should be considered when electrical devices such as pacemakers and defibrillators are used.
- Because TAMBOCOR slows cardiac conduction, pre-existing blocks may become more pronounced and subclinical blocks may become manifest.
- Correct electrolyte imbalances before treatment. These may cause or contribute to arrhythmias.
- Remember that impaired hepatic or renal function, including impairment associated with CHF, can contribute to elevated drug levels and necessitate special caution in dosing. The long half-life of flecainide along with the absence of a satisfactory method to remove the drug encourages one to begin dosing carefully and avoid overload with the drug. Careful gradation of dosing administration is of particular importance with TAMBOCOR CR capsules, where loading doses are specifically not recommended.
- It should also be noted that amiodarone may increase plasma flecainide concentrations.
- Treatment with TAMBOCOR should be monitored by frequent ECG recordings and/or plasma level monitoring as recommended.

Tablet dosage

Supraventricular arrhythmias

For patients with paroxysmal supraventricular arrhythmias, oral TAMBOCOR therapy may be started on an outpatient basis. The recommended starting dose is 50 mg every 12 hours. The dose may be increased in increments of 50 mg b.d. at intervals of at least four days until efficacy is achieved. Most patients do not require more than 150 mg every 12 hours (300 mg/day) which is the maximum recommended daily dose.

Ventricular arrhythmias
For patients with symptomatic sustained ventricular arrhythmias, oral TAMBOCOR therapy should be started in the hospital. The recommended starting dose is 100 mg every 12 hours. If clinical benefit is not achieved the dose may be increased in increments of 50 mg b.d. at intervals of at least four days until efficacy is achieved. The maximum recommended dose is 400 mg/day.

Once adequate control of the arrhythmia has been achieved, it may be possible in some patients to reduce the dose as necessary to minimise side effects or effects on conduction. In such patients, efficacy at the lower dose should be evaluated. An occasional patient not adequately controlled by, or intolerant to, a dose given at 12-hour intervals may be dosed at eight-hour intervals.

Amiodarone
As for many other anti-arrhythmic agents, in the presence of amiodarone, plasma levels of flecainide may be altered. Four situations may be encountered:

1. TAMBOCOR stopped and amiodarone started: Wait three plasma half-lives of flecainide (about 3 days) before starting amiodarone.

2. TAMBOCOR continued and amiodarone introduced. The dose of TAMBOCOR should be reduced to 50% at the same time as amiodarone is started. Plasma levels should be taken prior to and after amiodarone therapy is started. Based on therapeutic response and plasma levels, TAMBOCOR dosage can be adjusted accordingly. Avoid levels that exceed the therapeutic range of flecainide (0.2 to 1.0 µg/mL).

3. Amiodarone stopped and TAMBOCOR started: As the elimination of amiodarone is extremely slow, TAMBOCOR should be started at a dose of 50 mg b.d. Plasma level monitoring of flecainide should be done frequently. Based on therapeutic response and plasma levels the dosage of TAMBOCOR can be adjusted accordingly.

4. Amiodarone continued and TAMBOCOR started: When adding TAMBOCOR to the regimen of a patient on a stabilised and well tolerated dose of amiodarone, TAMBOCOR should be started at a dose of 50 mg b.d. and plasma level monitoring of flecainide should be done frequently. Based on therapeutic response and plasma levels, the dosage of TAMBOCOR can be adjusted accordingly. Increases in TAMBOCOR dosage should be made carefully in increments not exceeding 50 mg b.d. and only after levels of flecainide have been obtained. If the dosage of amiodarone is changed, again carefully monitor plasma levels of flecainide and adjust TAMBOCOR dosage accordingly.

<u>TAMBOCOR CR capsules</u>
The overall dosage guidance follows the same general approach as the conventional tablets. Owing to the drug-specific metabolism and elimination of flecainide, an optimal effect may not be achieved in steady state conditions for patients without dose restrictions (see below and section 4.4) until after about 7 days with TAMBOCOR CR. However, in patients with dose restrictions, the time to reach steady state conditions may take 2 to 3 weeks. TAMBOCOR CR should be administered gradually. Loading doses are not recommended. TAMBOCOR CR capsules should be taken with a glass of water during or after meals.

The normal recommended TAMBOCOR CR dose for patients of about 70 kg body weight is 100 mg/day. If necessary, the dose can be increased gradually using frequent ECG monitoring to a maximum of 300 mg/day. Dose increases should not exceed 100 mg. Dose increases should be made no more frequently than once every 7 days. For patients weighing considerably more or less than 70 kg, the dosage should be adjusted accordingly.

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

A low starting dose and cautious increases of dosage with ECG and plasma level monitoring will often be necessary for patients with renal impairment. In elderly patients the initial dosage of TAMBOCOR CR should be no more than 100 mg/day. The TAMBOCOR CR dosage for patients receiving concomitant amiodarone or cimetidine therapy should generally not exceed 200 mg/day. If TAMBOCOR CR is used in patients with pacemakers, the dosage should generally not exceed 200 mg/day due to possible effects on cardiac conduction (increase of endocardial pacing thresholds).

Structural heart disease
Use of TAMBOCOR in the presence of structural heart disease (SHD) is not advised. SHD is defined as ventricular dysfunction or hypertrophy, symptomatic ischaemic heart disease or valvular heart disease. SHD usually would not include haemodynamically insignificant valvular heart disease, mitral valve prolapse or treated hypertension.

ECG monitoring
Frequent and long-term ECG monitoring should be performed in all patients to guide dosage of TAMBOCOR. This applies to the initiation of therapy, changes in dosage and control of long-term therapy with TAMBOCOR. ECG monitoring should be performed at 2 to 4 day intervals at the beginning of therapy, and particularly following dose increases. Particular attention must be paid during ECG monitoring to possible widening of the QRS complex during treatment. If QRS widening occurs by more than 25% compared to baseline, the dosage should be reduced or TAMBOCOR discontinued until the ECG reverts to normal. Frequent ECG monitoring should also be performed to guide dosage if amiodarone or cimetidine is given in combination with TAMBOCOR.

Plasma level monitoring
Periodic monitoring of trough plasma levels may be useful in patient management. The large majority of patients successfully treated with TAMBOCOR were found to have trough plasma levels between 200 to 1000 ng/mL. Plasma levels above 700 to 1000 ng/mL are associated with increased likelihood of adverse experiences. The probability of adverse experiences, especially cardiac adverse experiences such as conduction defects or bradycardia, may increase with higher trough plasma levels, especially when these exceed 1000 ng/mL. Recognition of the correlation of plasma levels to proarrhythmic events associated with treatment of ventricular tachycardia appears to have led to a reduced frequency and severity of such events.

Plasma level monitoring is required in patients with renal failure or hepatic disease; since elimination of flecainide from plasma may be markedly slower. It should be borne in mind that in patients with renal or hepatic impairment, it may take longer than four days before a new steady-state plasma level is reached following a dosage change. Dosage adjustment may be necessary.

Monitoring of plasma levels is also strongly recommended in patients on concurrent amiodarone therapy and may be helpful in patients with congestive heart failure and in patients with moderate renal disease.

Children

TAMBOCOR is not recommended in children under 12 as there is insufficient evidence of its use in this age group. However, a considerable body of experiential evidence has accumulated which is strongly suggestive of the clinical effectiveness of TAMBOCOR in children of varying ages with supraventricular tachycardia but with structurally normal hearts. Similar empirical evidence of effectiveness exists for the use of TAMBOCOR in foetal tachyarrhythmias. There is an age dependent variability in the elimination half-life of flecainide in children and the available clinical evidence suggests an effective dose of TAMBOCOR in young patients, based either on body surface area or body weight, varies from 100 to 200 mg/m²/day or 1 to 8 mg/kg/day respectively. These daily doses were administered every 8 to 12 hours and adjusted according to patient age and trough plasma flecainide levels.

Elderly

From age 20 to 80, plasma flecainide levels are only slightly higher with advancing age. With usual doses the rate of flecainide elimination from plasma is somewhat slower in elderly than in younger subjects. This should be taken into consideration when making dose adjustments.

4.3 Contraindications

1. Structural heart disease.

2. Second or third degree AV block, unless a ventricular programmable pacemaker is present to sustain rhythm.

3. Right bundle branch block when associated with left hemiblock, unless a pacemaker is utilised to sustain rhythm.

4. Asymptomatic premature ventricular contractions and/or asymptomatic non-sustained ventricular tachycardia in patients with a history of myocardial infarction, cardiogenic shock and reduced cardiac output (LVEF <35%). This contraindication may be mitigated in patients with life-threatening ventricular arrhythmias.

5. Cardiogenic shock.

6. Post-myocardial infarction patients.

7. In patients with significant renal or hepatic impairment, unless potential benefits outweigh risks. If used, frequent plasma level monitoring is required to guide dosage.

8. Known hypersensitivity to flecainide or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Mortality

In the Cardiac Arrhythmia Suppression Trial (CAST), a long-term, large scale, multi-centre, double-blind, randomised, placebo-controlled clinical trial in patients with asymptomatic non-life threatening ventricular arrhythmias who had myocardial infarction more than six days but less than two years previously, oral flecainide was associated with a higher incidence of mortality or non-fatal cardiac arrest (19/323) as compared with its matching placebo (7/318). The average duration of treatment with flecainide in this study was 10 months. In that same study, an even higher incidence of mortality was observed in flecainide-treated patients with more than one myocardial infarction. While there are no comparable mortality trial data for other Class I antiarrhythmic agents post myocardial infarction, meta-analysis of small-scale clinical trials of these agents in similar populations suggests a trend towards increased mortality compared to placebo. In the light of this information, it is prudent to consider the prophylactic use of Class I antiarrhythmic drugs following myocardial infarction as potentially hazardous. Indeed, the use of these agents for other than life-threatening arrhythmias or severe symptoms due to arrhythmias, is not recommended. Comparable placebo-controlled clinical trials have not been done to determine if flecainide is associated with a higher risk of mortality in other patient groups.

Structural Heart Disease

Patients with structural heart disease, treated with TAMBOCOR for supraventricular arrhythmias, may be at increased risk for proarrhythmia and cardiac adverse events. The use of TAMBOCOR in these patients has been associated with life-threatening and occasionally fatal ventricular arrhythmias. Therefore, in these patients, especially in the presence of impaired left ventricular function with ejection fraction ≤ 40%, TAMBOCOR should be used with extreme caution, preferably after other antiarrhythmic drugs have been tried or considered inappropriate.

Ventricular Proarrhythmic Effects in Patients with Atrial Fibrillation /Flutter

A review of the world literature revealed reports of 568 patients treated with oral TAMBOCOR (flecainide acetate) for paroxysmal atrial fibrillation/flutter (PAF). Ventricular tachycardia was experienced in 0.4% (2/568) of these patients. Of 19 patients in the literature with chronic atrial fibrillation, 10.5% (2/19) experienced ventricular tachycardia or ventricular fibrillation.

FLECAINIDE IS NOT RECOMMENDED FOR USE IN PATIENTS WITH CHRONIC ATRIAL FIBRILLATION. Case reports of ventricular proarrhythmic effects in patients treated with TAMBOCOR for atrial fibrillation/flutter included increased premature ventricular contractions (PVCs), ventricular tachycardia (VT), ventricular fibrillation (VF) and death.

As with other class I agents, patients treated with TAMBOCOR for atrial flutter have been reported with 1:1 atrioventricular conduction due to slowing of the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive TAMBOCOR. Concomitant negative chronotropic therapy such as digoxin or ß-blockers may lower the risk of this complication.

Proarrhythmic Effects

As with other antiarrhythmic drugs TAMBOCOR has been associated with the development of new or worsened arrhythmias. These so-called proarrhythmic effects may range in severity from an increase in frequency of PVCs to the development of more severe forms of ventricular tachycardia. In a few patients TAMBOCOR has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. The incidence of proarrhythmic events was higher in studies of patients treated for recurrent ventricular tachycardia, often with coexisting congestive heart failure, than in studies of patients treated for stable ventricular ectopy. Treatment with any antiarrhythmic agent should be initiated in hospital in patients treated for recurrent sustained ventricular tachycardia, especially those with congestive heart failure or low ejection fractions. Effective use of TAMBOCOR may be assisted in some patients by electrophysiological investigation.

Heart failure

Because TAMBOCOR has a mild negative inotropic effect, it may cause or worsen congestive heart failure, particularly in patients with cardiomyopathy, pre-existing severe heart failure (NYHA functional class III or IV) or ejection fractions ≤ 40%. TAMBOCOR should, therefore, be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dose should be no more than 100 mg b.d. (see "Dosage and Administration") and they should be monitored carefully. Careful attention must be given to maintenance of cardiac function, including optimisation of digitalis, diuretic or other therapy. In the cases where congestive heart failure has occurred during TAMBOCOR therapy, the onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretic, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 µg/mL.

Effects on cardiac conduction

TAMBOCOR slows cardiac conduction sufficiently in most patients to produce measurable increases in the duration of the PR, QRS and QT intervals on the electrocardiogram. This is an extension of the pharmacological action of the drug and most patients experience no detrimental clinical effects from these changes in conduction. Increases of more than 25% in the duration of the PR interval occur commonly and approximately one third of patients may develop first-degree heart block (PR interval greater than or equal to 0.20 seconds). Widening of the QRS of 25% or more is also common and many patients develop QRS complexes with a duration of 0.12 seconds or more. The QT (uncorrected) interval widens about 8% on the average, mostly due to the widening of the QRS. (The JT interval [QT minus QRS] is usually unaffected or widens about 4%).

Although clinically significant conduction changes such as sinus pause, sinus arrest, second or third degree AV block occasionally occur, an attempt should be made to reduce the dosage of TAMBOCOR (see section 4.2) to the lowest effective dose in an effort to minimise these effects. If second or third-degree AV block, or right bundle branch block associated with a left hemi-block occur, TAMBOCOR therapy should be discontinued unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker.

Sick sinus syndrome (Bradycardia-tachycardia syndrome)
TAMBOCOR should not be used in patients with advanced sinus node disease and should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest. Pacing rescue facilities should be available.

Digitalis intoxication
TAMBOCOR has not been evaluated in the treatment of arrhythmias secondary to digitalis intoxication and it increases the plasma level of digoxin (see section 4.5), therefore it is not recommended for such use.

Electrolyte disturbances
The presence of a potassium excess or deficit may alter the effects of Class I antiarrhythmic drugs. Any pre-existing hypokalaemia or hyperkalaemia or other electrolyte disturbances should be corrected before administration of TAMBOCOR.

Effects on pacemaker thresholds
TAMBOCOR is known to reversibly increase endocardial pacing thresholds and may suppress ventricular escape rhythms. It should 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. It is suggested that the threshold in patients with pacemakers be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multi-programmable pacemakers and when these changes occur, usually a doubling of either voltage or pulse width is sufficient to regain capture.

Concomitant antiarrhythmic therapy
Due to limited exposure, the concomitant use of TAMBOCOR and other antiarrhythmic agents is not recommended.

Both disopyramide and verapamil have negative inotropic properties and the effects of co-administration with TAMBOCOR are unknown. Neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR, unless, in the judgement of the physician, the benefit of this combination outweighs the risks.

Formal interaction studies have not been conducted with amiodarone and TAMBOCOR. However, clinical experience indicates, as for many other antiarrhythmic agents, that amiodarone can increase plasma levels of flecainide. If in the judgement of the physician the benefits outweigh the risks and TAMBOCOR is to be administered in the presence of amiodarone, the dose of TAMBOCOR should be reduced (see section 4.2) with plasma flecainide monitoring.

Lidocaine has been used occasionally with TAMBOCOR while awaiting the therapeutic effect of TAMBOCOR. No adverse drug interactions were apparent. However, no studies have been performed to demonstrate the usefulness of this regimen.

Alkaline urine

In the presence of alkaline urine (pH greater than 7.0) which may result from diet, concomitant medication or disease states, TAMBOCOR elimination may be slower, as has also been reported for other basic compounds and TAMBOCOR dosage may need to be reduced.

Renal impairment

Renal impairment requires particular caution during treatment with TAMBOCOR.

A lower starting dose at half the usual dosing recommendations, cautious increases of dosage and plasma level monitoring will often be necessary for patients with significant renal disease (creatinine clearance corrected for body surface area of <35 mL/min/1.73 m²). In patients with less severe renal disease the initial dosage may be as great as 100 mg every 12 hours. When used in such patients, frequent plasma level monitoring is strongly recommended to guide dosage adjustments. In both groups of patients, dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days with TAMBOCOR tablets), observing the patient closely for signs of adverse cardiac effects or other toxicity.

Hepatic impairment

Manifest hepatic functional impairment (liver failure) requires particular caution during treatment with TAMBOCOR.

Since elimination of flecainide from plasma can be markedly slower in patients with significant hepatic impairment, treatment with TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma flecainide level monitoring is required to guide dosage and increases should be made very cautiously when plasma levels have reached a plateau.

Blood dyscrasias

There have been extremely rare reports of blood dyscrasias (pancytopenia, anaemia, thrombocytopenia, leukopenia, granulocytopenia). Although no causal relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.

Lung disease

There have been very rare reports of lung disease (pulmonary fibrosis, interstitial lung disease and pneumonitis). Although no causal relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop lung disease in order to eliminate TAMBOCOR as the possible causative agent.

4.5 Interaction with other medicines and other forms of interaction

Digoxin

During multiple oral dosage of TAMBOCOR to healthy subjects stabilised on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours post dose. These small changes in digoxin levels should be of no clinical consequence for patients receiving chronic digoxin therapy. TAMBOCOR has been administered to patients receiving digitalis preparation without adverse effects.

ß-adrenergic blocking agents
TAMBOCOR has been administered to patients receiving ß-adrenergic blocking agents without adverse effects. In a formal interaction study conducted in healthy males receiving TAMBOCOR and propranolol concurrently, plasma TAMBOCOR levels were about 20% higher and propranolol levels about 30% higher, in comparison to control values. These small changes should be of no clinical consequence. In this study, TAMBOCOR and propranolol were each found to have slight negative inotropic effects on cardiac function; when administered together these effects were never any more than additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. While these effects were of little clinical consequence in healthy subjects, the possibility of exaggerated effects from this combination in patients with reduced left ventricular function should be borne in mind. In TAMBOCOR clinical trials, patients who were receiving ß-blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of ß-blockers and flecainide should be recognised.

Anti-arrhythmics
See section 4.4 "Concomitant antiarrhythmic therapy".

Nifedipine, diltiazem
There has been too little experience with the co-administration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.

Diuretics
TAMBOCOR has been used in large numbers of patients receiving diuretics without apparent interactive effects.

Cimetidine
In healthy subjects receiving cimetidine (1 g daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.

Other medicines
Although formal interaction studies have not been conducted with TAMBOCOR and other drugs, TAMBOCOR is not extensively bound to plasma proteins and consequently interactions with other drugs which are highly protein bound (e.g. anticoagulants) would not be expected.

Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination.

Cytochrome P4502D6 metabolism
The biotransformation of flecainide is catalysed by cytochrome P4502D6 and is subject to genetic polymorphism. This is further complicated by the influence of renal excretion. In poor metabolisers, especially those with renal impairment, flecainide will tend to reach higher plasma concentrations. However, in extensive metabolisers, again especially in subjects with renal impairment, drugs that inhibit cytochrome P4502D6 might increase the plasma concentrations of flecainide during chronic therapy. Furthermore, flecainide is itself an inhibitor of cytochrome P450IID6 and may contribute to such increases in its own plasma levels.

Alcohol
No information available

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3

Flecainide has been shown to have teratogenic effects (e.g. club paws, sternebral and vertebral abnormalities, pale hearts with contracted ventricular septa) and an embryotoxic effect (e.g. increased resorptions) in one breed of rabbit (New Zealand White) but not in another (Dutch Belted), when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats or mice given doses up to 50 and 80 mg/kg/day, respectively, however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Although the significance of these findings to humans is uncertain, since there is no information on the effect on the human foetus, TAMBOCOR should not be used during pregnancy unless as a drug of last resort in life-threatening arrhythmias.

Labour and Delivery
It is not known whether the use of TAMBOCOR during labour or delivery has immediate or delayed adverse effects on the mother or foetus, affects the duration of labour or delivery or increases the possibility of forceps delivery or other obstetrical intervention.

Lactation
No specific studies are available to determine the excretion of TAMBOCOR in human breast milk. However, limited data indicate that flecainide is excreted in breast milk. The benefit of TAMBOCOR during lactation should therefore be weighed against possible effects on the child.

4.7 Effects on ability to drive and use machines

Since TAMBOCOR can cause dizziness, light headedness, faintness and visual disturbance, patients should be cautioned about engaging in activities requiring judgement and physical coordination (such as driving an automobile or operating dangerous machinery) when these effects occur.

4.8 Undesirable effects

Patients with ventricular arrhythmias
TAMBOCOR has been evaluated in 1,224 patients participating in clinical trials which included both life threatening and non-life threatening ventricular arrhythmias. The most serious adverse reactions reported for TAMBOCOR in patients with ventricular arrhythmias were new or exacerbated ventricular arrhythmias which occurred in 6.8% of patients and new or worsened congestive heart failure which occurred in 3.9% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. A total of 1.2% of patients developed sinus bradycardia, sinus pause, or sinus arrest (see section 4.4). The frequency of most of these serious adverse reactions probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/mL.

The most commonly reported non-cardiac reactions experienced by patients with ventricular arrhythmias were dizziness 27%, visual disturbance 26% (includes blurred vision, diplopia, visual field effects, photophobia), headache 10%, nausea 10% and dyspnoea 9%. Other adverse reactions occurring in over 3% of the patients in clinical trials: *Body as a Whole* - fatigue 7%, asthenia 5%; *Cardiovascular* - palpitations 6%, chest pain 6.%; *Gastrointestinal* - constipation 4%, abdominal pain 3%; *Nervous System* - tremor 6%, nervousness 3%, paraesthesia 3%; *Skin* - rash 4%.

The following additional adverse reactions, possibly related to TAMBOCOR therapy and occurring in 1 to less than 3% of patients have been reported in clinical trials: *Body as a Whole* - pain, increased sweating, flushing, dry mouth, swollen lips, tongue and mouth, eye pain and irritation, arthralgia, fever, myalgia, hemiparesis, weakness; *Cardiovascular* - oedema, syncope, tachycardia, angina pectoris, conduction disturbance; *Gastrointestinal* - vomiting, diarrhoea, anorexia; *Nervous System* - hypoaesthesia, somnolence, insomnia, ataxia, depression; *Respiratory* - coughing; *Skin* - pruritus; *Special Senses* - tinnitus; *Urinary System* - micturition disorder (includes urinary retention, frequency, polyuria, dysuria).

The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole* - impotence, decreased libido, gynaecomastia, malaise, vertigo; *Cardiovascular* - bradycardia, EC abnormality, hypertension, hypotension, heart disorder, myocardial infarction, peripheral ischaemia, pulmonary oedema; *Gastrointestinal* - dyspepsia, flatulence, GI haemorrhage; *Nervous System* - anxiety, twitching, convulsions, nystagmus, stupor, dysphonia, speech disorder, coma, amnesia, confusion, depersonalisation, hallucination, paranoid reaction, euphoria, apathy, morbid dreams; *Respiratory* - bronchospasm, laryngismus; *Skin* - dermatitis, hypertrichosis, photosensitivity reaction, skin discolouration; *Special Senses* - deafness, parosmia, loss of taste, taste perversion; *Urinary System* - renal failure, haematuria; *Laboratory Abnormalities* - hyperglycaemia, increased nonprotein nitrogen, increased serum alkaline phosphatase, increased serum SGPT and SGOT. Patients with elevations of liver function tests have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established.

Adverse reactions leading to discontinuation of therapy occurred in 18.5% of the patients. The two most common were non-cardiac adverse reactions 9.0% and new or worsened arrhythmias 6.8%.

<u>Patients with supraventricular arrhythmias</u>
TAMBOCOR has been evaluated in 225 patients with supraventricular arrhythmias. The most serious adverse reactions reported for TAMBOCOR in patients with supraventricular arrhythmias were new or worsened supraventricular or ventricular arrhythmias which were reported in 4% of patients (see section 4.4), conduction disturbance which occurred in 2% of patients and new or worsened congestive heart failure which occurred in 0.4% of patients.

The most commonly reported non-cardiac adverse reactions for supraventricular arrhythmia patients remain consistent with those known for patients treated with TAMBOCOR for ventricular arrhythmias: vision disturbance 38%, dizziness 37%, headache 18%, nausea 18%, dyspnoea 13%, fatigue 13%, chest pain 12%, palpitations 11%. Although these incidences are higher than those reported in ventricular arrhythmia patients it is difficult to compare supraventricular and ventricular data bases because many of the supraventricular arrhythmia patients were dosed to tolerance in the clinical trials.

Post-marketing experience
In post-marketing surveillance experience, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, very rare reports of pulmonary fibrosis, interstitial lung disease and pneumonitis, and extremely rare reports of blood dyscrasias (see section 4.4). Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in these patients in order to eliminate TAMBOCOR as the possible causative agent.

Cardiovascular/pro-arrhythmic effects
Pro-arrhythmic effects occur but are most likely in patients with structural heart disease and/or significant left ventricular impairment. AV heart block, angina pectoris, hypertension and hypotension have been reported. The most serious adverse effects reported for TAMBOCOR are new or exacerbated ventricular arrhythmias and new or worsened congestive heart failure. In some patients, flecainide treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. Rare occurrences of second or third-degree AV block, sinus bradycardia, sinus pause or sinus arrest have been reported. 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 TAMBOCOR Injection for conversion of acute arrhythmias. This effect is usually short lived and abates quickly following cessation of therapy.

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms
No data are available concerning overdosage of TAMBOCOR in humans. However, animal studies suggest the following events may occur: lengthening of the PR interval; increases in the QRS duration, QT interval and amplitude of the T-wave; a reduction in myocardial rate and contractility; conduction disturbances; hypotension; and death from respiratory failure or asystole.

Management
Treatment of overdosage should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoprenaline; mechanically assisted respiration; circulatory assistance such as intra-aortic balloon pumping and transvenous pacing in the event of conduction block. Because of the long plasma half-life of TAMBOCOR (range from 12 to 27 hours in patients), these supportive treatments may need to be continued for extended periods of time. Haemodialysis is not an effective means of removing TAMBOCOR from the body.

For the treatment of TAMBOCOR overdose when urine is clearly alkaline, acidification of urine (e.g. with ammonium chloride) may promote TAMBOCOR elimination. When urine is not clearly alkaline, it may be of some benefit to empirically acidify the urine in severe overdose cases.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Flecainide acetate has local anaesthetic activity and belongs to the membrane stabilising (Class I) group of antiarrhythmic agents. It has electro-physiological effects characteristic of the IC (fast inward sodium channel blockers) class of antiarrhythmics.

TAMBOCOR produces a dose related decrease in intracardiac conduction in all parts of the heart with the greatest effect on the His-Purkinje system (H-V conduction). Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times, although present, are less pronounced than those on ventricular conduction velocity. Significant effects on refractory periods are observed in the atria and ventricles. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths are somewhat increased. This latter effect may become significant in patients with sinus node dysfunction.

TAMBOCOR affects the electrocardiograph (ECG) by widening the PR interval and by prolonging the duration of the QRS complex. The widened QRS complex (ventricular depolarisation) results in a longer QT interval but there is little specific effect on the JT interval (ventricular repolarisation).

TAMBOCOR does not usually alter heart rate, although bradycardia and tachycardia have been reported occasionally. Decreases in ejection fraction, consistent with a negative inotropic effect, have been observed after single dose administration of 200 to 250 mg of flecainide in man in multiple dose studies, and exacerbations of clinical congestive heart failure (CHF) have been documented. Increases in ejection fraction may result from restoring normal rhythm.

Supraventricular arrhythmia

In patients with symptomatic paroxysmal atrial fibrillation and flutter, TAMBOCOR prolongs the time to the first recurrence as well as the interval between recurrences of these tachyarrhythmias.

Ventricular arrhythmia

TAMBOCOR causes a dose-related and plasma-level related decrease in single and multiple premature ventricular complexes (PVCs) and chronic therapy can suppress recurrence of ventricular tachycardia. In limited studies of patients with a history of ventricular tachycardia, flecainide has been successful 30 to 40% of the time in fully suppressing the inducibility of arrhythmias by programmed electrical stimulation.

5.2 Pharmacokinetic properties

Following oral administration, the absorption of flecainide from TAMBOCOR tablets is nearly complete. Peak plasma levels are reached after about three hours in most individuals (range 1 to 6 hours). Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacids do not affect absorption.

In studies of healthy subjects the apparent plasma half-life of flecainide averages 13 hours and is quite variable (range 7 to 22 hours). In studies involving patients with chronic PVCs, the apparent plasma half-life after multiple oral doses averaged about 20 hours and was also quite variable (range 12 to 27 hours). With multiple dosing, flecainide accumulates to steady-state plasma levels within 3 to 5 days, but once at steady state no additional or unexpected accumulation of drug in plasma occurs during chronic treatment. Plasma levels in an individual are approximately proportional to dose over the usual therapeutic range, deviating upwards from linearity only slightly (about 10 to 15% per 100 mg on average).

TAMBOCOR CR provides prolonged and essentially complete drug absorption which allows for once daily dosing and very sustained, flat plasma level profiles. Peak plasma levels are attained after about 13 hours (range 10.5 to 15.5 hours) following oral administration during long term therapy with TAMBOCOR CR. The apparent plasma half-life averages about 20 hours and is quite variable after multiple oral doses (range 12 to 27 hours). Plasma levels increase with multiple dosing, because of the long half-life, with steady-state levels being attained in 3 to 7 days.

Bioavailability studies with TAMBOCOR CR capsules compared with TAMBOCOR tablets have shown that the controlled-release form of administration is almost completely bioavailable. The same study also demonstrated that steady state plasma levels of flecainide were achieved by day 5 of treatment. Changeover from TAMBOCOR tablets to TAMBOCOR CR can then be conducted without re-instigation of dose-finding.

Following a single intravenous dose of TAMBOCOR injection plasma flecainide levels decrease rapidly during the initial 15 to 60 minutes distribution phase, then the rate of disappearance from plasma is relatively slow (half-life 7 to 15 hours).

In healthy subjects, about 30% of a single oral dose (range 10 to 50%) is excreted in urine as unchanged drug. The two major urinary metabolites are 2,5-dealkylated flecainide (active, but about one fifth as potent) and the 2,5-dealkylated lactam of flecainide (inactive metabolite). These two primarily conjugated metabolites account for most of the remaining portion of the dose. Several minor metabolites (3% of the dose or less) are also found in urine. Only 5% of the dose is excreted in faeces. Free (unconjugated) plasma levels of the two major metabolites in patients are very low (less than 50 ng/mL).

The elimination of flecainide from the body depends on renal function. With increasing renal impairment, the extent of unchanged flecainide excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Elimination of flecainide in these circumstances is linked more closely to its cytochrome P450IID6 dependent hepatic metabolism. Since flecainide is extensively metabolised, there is no simple relationship between renal function, creatinine clearance corrected for body surface area and the rate of flecainide elimination from plasma.

In patients with NYHA class III CHF, the rate of flecainide elimination from plasma is moderately slower (mean half-life 19 hours) than for healthy subjects (mean half-life 14 hours), but similar to the rate for patients with PVCs without CHF. The extent of excretion of unchanged drug in urine is also similar.

Haemodialysis removes only about 1% of an oral dose as unchanged flecainide. The extent of flecainide binding to human plasma proteins is about 40% and is independent of plasma level over the range of 15 to about 3400 ng/mL. Clinically significant medicine interactions based on protein binding effects would therefore not be expected.

Food
Food does not affect either the rate or extent of TAMBOCOR absorption.

5.3 Preclinical safety data
See section 4.6

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet 50 mg
Crosscarmellose sodium
Hydrogenated vegetable oil
Magnesium stearate
Microcrystalline cellulose
Pregelatinised maize starch

The tablet formulations are colour-free, preservative-free, sugar-free and do not contain gluten or lactose.

Capsule (100 mg and 200 mg)
Gelatin
Iron oxide black
Macrogol 400
Methacrylic acid copolymer
Microcrystalline cellulose
Opacode black S-1-277002
Purified talc
TekPrint black SW-9008
Titanium dioxide
Erythrosine (200 mg capsules only)

The capsule formulations are preservative-free, sugar-free and does not contain gluten or lactose.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

Tablets

50 mg tablets: 36 months

100 mg tablets: 60 months

Capsules

100 mg capsules: 36 months

200 mg capsules: 36 months

300 mg capsules: 36 months

6.4 Special precautions for storage

Store below 30^0C.

6.5 Nature and contents of container

Tablets

Blister foil strip packs: 60 tablets

Capsules

Blister foil strip packs: 30 capsules

6.6 Special precautions for disposal

Not applicable

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

iNova Pharmaceuticals (New Zealand) Limited
c/- Simpson Grierson
88 Shortland Street,
Auckland 1141

Toll free 0508 375 394

9 DATE OF FIRST APPROVAL

8 May 1989 (50 mg tablets)
20 September 1984 (100 mg tablets)
29 July 1993 (100 mg, 200 mg and 300 mg capsules)

10 DATE OF REVISION OF THE TEXT

20 October 2022

*Not currently supplied

NEW ZEALAND DATA SHEET
TAMBOCOR™ Tablets
TAMBOCOR™ CR Capsules

SUMMARY TABLE OF CHANGES

Date	Change
8 March 2018	Data sheet reformatted Section 4.2: Added TAMBOCOR tablets and TAMBOCOR CR capsules are for oral administration. Section 4.3: Added "or to any the excipients listed in section 6.1" to the hypersensitivity contraindication. Section 4.4: Cytochrome P450IID6 Metabolism precaution moved to section 4.5. Cytochrome P450IID6 changed to cytochrome P4502D6 Section 8: Change in sponsor name & address Added * not currently supplied (for Tambocor 100 mg tablets and Tambocor CR 300 mg capsules)
5 May 2022	Section 3: Removed reference to "3M" on tablet product descriptions
20 Oct 2022	Section 4.4: *Special warnings and precautions for use* (renal impairment) & section 5.2*: Pharmacokinetic properties* – changed wording from "creatinine clearance" to "creatinine clearance corrected for body surface area"