

Revised: October 2011 (14th version)

Standard Commodity Classification No. of Japan
872129

- Drug for tachyarrhythmia -
<Flecainide acetate Tablets, JP>

Tambocor[®] Tablets 50mg
Tambocor[®] Tablets 100mg

Powerful drug and Prescription drug

Storage
TAMBOCOR should be stored at room temperature. TAMBOCOR bottled tablets should be protected from moisture after opening cap. (Tablets may become discolored with moisture.)

Expiration date
TAMBOCOR should be used before the expiration date indicated on the package or label.

	Tablets 50 mg	Tablets 100 mg
Approval No.	20300AMZ00442000	20300AMZ00443000
Date of listing in the NHI reimbursement price	Aug 1991	Aug 1991
Date of initial marketing in Japan	Aug 1991	Aug 1991
Date of latest reexamination	Mar 1999	
Date of latest approval of indications	May 2010	

Caution : Use only as directed by a physician.

CONTRAINDICATIONS (TAMBOCOR is contraindicated in the following patients.)

- Patients with congestive heart failure
[TAMBOCOR may aggravate symptoms of heart failure due to its negative inotropic action.]
- Patients with severe atrioventricular (AV) block or severe sinoatrial (SA) block
[Since TAMBOCOR inhibits AV and SA conduction, conduction disturbances may be aggravated.]
- Patients with asymptomatic ventricular extrasystole or non-sustained ventricular tachycardia after myocardial infarction
[The CAST clinical trial on sudden death reported an increase in mortality rate for such patients who took TAMBOCOR. See "Other Precautions" section.]
- Pregnant women or women suspected of being pregnant
[See "Use during Pregnancy, Delivery or Lactation" Section.]
- Patients on ritonavir therapy
[See "Drug Interactions" section.]
- Patients on mirabegron therapy
[See "Drug Interactions" Section.]

DESCRIPTION

1. Composition

Tablets 50 mg:

Each white plain tablet contains 50 mg of flecainide acetate. It also contains croscarmellose sodium, microcrystalline cellulose, hydrogenated oil, magnesium stearate and partly pregelatinized starch as inactive ingredients.

Tablets 100 mg:

Each white plain tablet contains 100 mg of flecainide acetate.

It also contains croscarmellose sodium, microcrystalline cellulose, hydrogenated oil, magnesium stearate and partly pregelatinized starch as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
TAMBOCOR Tablets 50 mg	Plain tablets				White, faint odor like acetic acid.
	E 237	Diameter (mm) 7.1	Weight (mg) 132	Thickness (mm) 3.3	
TAMBOCOR Tablets 100 mg	Plain tablets				White, faint odor like acetic acid.
	E 238	Diameter (mm) 8.6	Weight (mg) 264	Thickness (mm) 4.5	

INDICATIONS

The following conditions where other antiarrhythmic drugs cannot be used or are ineffective:

Adults:

Tachyarrhythmia (Paroxysmal atrial fibrillation/flutter, ventricular)

Infants, toddlers, and children:

Tachyarrhythmia (Paroxysmal atrial fibrillation/flutter, paroxysmal supraventricular, ventricular)

<Precautions>

When TAMBOCOR is administered to infants, toddlers and children, its use must be supervised by a doctor who is adept in the treatment of pediatric arrhythmia.

In the case of atrial flutter and ventricular tachycardia, both of which accompany underlying heart disease, TAMBOCOR should only be used if the expected therapeutic benefits outweigh the possible risks associated with treatment.

DOSAGE AND ADMINISTRATION

Adults:

Tachyarrhythmia (paroxysmal atrial fibrillation/flutter)

The usual initial adult dose is 100 mg of flecainide acetate daily. If the effect is insufficient, the dose may be increased up to 200 mg daily, which should be administered in two divided doses. The dose may be reduced depending on the patient's age and symptoms.

Tachyarrhythmia (ventricular)

The usual initial adult dose is 100 mg of flecainide acetate daily. If the effect is insufficient, the dose may be increased up to 200 mg daily, which should be administered in two divided doses. The dose may be adjusted depending on the patient's age and symptoms.

Infants, toddlers, and children:

Tachyarrhythmia (Paroxysmal atrial fibrillation/flutter, paroxysmal supraventricular, ventricular)

The usual oral dosage for infants 6 months old or over, toddlers, and children is 50-100 mg/m² (body surface area) of flecainide acetate daily in two to three divided doses. The dose may be adjusted depending on the patient's age and symptoms. The maximum dose is 200 mg/m² daily.

The usual oral dosage for infants under the age of 6 months is 50 mg/m² (body surface area) of flecainide acetate daily in two to three divided doses. The dose may be adjusted depending on the patient's age and symptoms. The maximum dose is 200 mg/m² daily.

PRECAUTIONS

1. Careful Administration (TAMBOCOR should be administered with care in the following patients.)

- (1) Patients who have an underlying heart disease (myocardial infarction, valvular disease, cardiomyopathy, etc.)
[TAMBOCOR may aggravate cardiac function due to its negative inotropic action.]
- (2) The elderly [See "Use in the Elderly" section.]
- (3) Patients with conduction disturbances (AV block, SA block, bundle branch block, etc.)
[Since TAMBOCOR inhibits AV conduction and SA conduction, etc., conduction disturbances may be aggravated.]
- (4) Patients with marked sinus bradycardia
[TAMBOCOR may inhibit sinus node function.]
- (5) Patients with a history of congestive heart failure
[TAMBOCOR may aggravate cardiac function due to its negative inotropic action.]
- (6) Patients with hepatic function disorders
[Since TAMBOCOR is metabolized in the liver, such patients may suffer overdosage.]
- (7) Patients with serious renal function disorders
[Since TAMBOCOR is excreted through the kidney, such patients may suffer overdosage.]
- (8) Patients with hypokalemia
[Such patients are likely to experience a proarrhythmic effect, causing severe arrhythmia.]

2. Important Precautions

- (1) The use of TAMBOCOR should be considered only in cases where other antiarrhythmic drugs cannot be used or are ineffective.
- (2) Patients on TAMBOCOR should be observed frequently and monitored regularly for ECG, heart rate, blood pressure and cardiothoracic ratio. If abnormal findings, such as prolongation of PQ interval, QRS widening, prolongation of QT interval, bradycardia or decrease in blood pressure, are observed, the dosage should be reduced or the treatment discontinued immediately. Especially, when administering TAMBOCOR to the following patients, appropriate precautions such as starting at a low dosage should be taken, and ECG should be monitored frequently.

It has been reported that torsades de pointes and Adams-Stokes syndrome occurred during the administration of TAMBOCOR.

- 1) Patients who have underlying heart disease (myocardial infarction, valvular disease, cardiomyopathy, etc.) and may experience heart failure
[TAMBOCOR may aggravate cardiac function due to its negative inotropic action. In addition, when TAMBOCOR is used for patients with ventricular arrhythmia, they should be hospitalized for 1 or 2 weeks after being started on TAMBOCOR because of the high risk of aggravating ventricular tachycardia, ventricular fibrillation, etc.]
- 2) The elderly
[Since adverse reactions may occur, TAMBOCOR should be administered with great care in the elderly. In addition, when TAMBOCOR is used for patients with ventricular arrhythmia, they should be hospitalized before being started on TAMBOCOR. See "Use in the Elderly" section.]
- 3) Coadministration with other antiarrhythmic drugs
[No efficacy or safety has been established.]
- 4) Patients with renal function disorders
[Since TAMBOCOR is eliminated from the body through the kidney, its blood concentration is likely to be elevated. See "PHARMACOKINETICS" section.]
- (3) For patients with serious renal function disorders (creatinine clearance ≤ 20 mL/min), it is recommended not to exceed the daily dose of 100 mg (50 mg twice daily) because the plasma drug concentration may increase to unexpectedly high levels in such patients.
- (4) TAMBOCOR may increase the cardiac pacing threshold. Caution should be taken when administering TAMBOCOR to permanently or temporarily paced patients. In addition, the pacing threshold should be measured at proper intervals in paced patients. In the case of any abnormal findings, the dosage should be reduced or the treatment discontinued immediately.
- (5) Caution should be exercised when the daily dose of 200 mg is exceeded, because plasma flecainide concentrations may increase to an unexpectedly high level, which may increase the risk of adverse reactions.

- (6) Since proarrhythmia may occur frequently when the dosage of TAMBOCOR is increased, adequate caution should be exercised.
- (7) Since patients are at high risk of induction of sinus arrest and sick sinus syndrome when an attack ceases, caution should be exercised when TAMBOCOR is used for patients with paroxysmal atrial fibrillation/flutter.
- (8) If psychoneurologic symptoms, such as dizziness or light-headedness, etc. appear or tend to be aggravated during treatment, the dosage should be reduced or the treatment discontinued immediately.
- (9) It has been reported that the use of TAMBOCOR in Brugada syndrome was brought about characteristic changes on the ECG (right bundle branch block and ST segment elevation of right chest leads (V₁~V₃)). Caution should be exercised with respect to ventricular fibrillation, ventricular tachycardia, ventricular extrasystolic contraction etc.
- (10) Since the ingestion of breast milk or dairy products inhibits absorption of TAMBOCOR, and reduces its efficacy, special attention is required when TAMBOCOR is administered to infants. Additionally, adequate attention should be paid to increases in the blood concentration of TANBOCOR when patients discontinue ingesting breast milk or dairy products. (See “Blood concentration” section.)

3. Drug Interactions

TAMBOCOR is metabolized mainly by CYP2D6. [See “PHARMACOKINETICS” Section.]

1) Contraindications for coadministration (TAMBOCOR should not be coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Ritonavir (Norvir)	Serious adverse reactions such as arrhythmias, blood dyscrasia or convulsion, etc. may occur.	The blood flecainide concentration is expected to increase sharply due to competitive inhibition of cytochrome P450 by ritonavir.
Mirabegron (Betanis)	QT prolongation and ventricular arrhythmias (including torsades de pointes) may occur.	Flecainide and mirabegron have proarrhythmic potential. Blood flecainide concentrations may increase due to the cytochrome P450 (CYP2D6) inhibiting action of mirabegron.

2) Precautions for coadministration (TAMBOCOR should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Digitalis glycoside Digoxin Digitoxin Deslanoside, etc.	Blood concentration of digoxine, digitoxin and deslanoside may increase.	Mechanism unknown

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
β-Blockers Propranolol hydrochloride, etc.	Cardiac function may be impaired or AV block may occur. In addition, when concomitantly administered with propranolol, blood concentrations of flecainide and propranolol may increase.	Both flecainide and β-blockers (propranolol, etc.) mutually exhibit a negative inotropic action and atrioventricular conduction inhibiting action. In addition, since both flecainide and propranolol are substrates of CYP2D6, they competitively inhibit the metabolism of each other.
Paroxetine hydrochloride hydrate	Blood flecainide concentration may increase.	Since paroxetine inhibits CYP2D6, blood flecainide concentration may increase.
Cimetidine Quinidine sulfate hydrate	Blood flecainide concentration may increase.	Based on inhibition of cytochrome P450 by cimetidine and quinidine.
Phenytoin Phenobarbital Carbamazepine	Blood flecainide concentration may decrease.	Based on induction of hepatic drug metabolizing enzymes by phenytoin, phenobarbital and carbamazepine.
Amiodarone hydrochloride	It has been reported that coadministration with amiodarone produces a 1.5-fold increase in blood flecainide concentration. Therefore, the dosage of TAMBOCOR should be reduced to 2/3 of the usual dosage.	Mechanism unknown
Calcium channel blockers Verapamil hydrochloride, etc.	Failed cardiac function or AV block may occur.	Both TAMBOCOR and calcium channel blockers (verapamil, etc.) have negative inotropic actions and inhibit AV conduction.
Lidocaine hydrochloride Procainamide hydrochloride	It has been reported that antiarrhythmic activity or toxic symptoms are enhanced in experimental arrhythmia models.	Mechanism unknown

4. Adverse Reactions

- Tachyarrhythmia (paroxysmal atrial fibrillation/flutter)
Adverse reactions were reported in 53 of 268 patients (19.78%) in clinical studies (to the time of approval). Adverse reactions were reported in 85 of 552 patients (15.40%) in post-marketing surveillance conducted for the additional indications (as of the end of the surveillance).
- Tachyarrhythmia (ventricular)
Adverse reactions were reported in 265 of 2,929 patients (9.05%) in clinical studies and treatment outcome study (as of the end of reexamination).

(1) Clinically significant adverse reactions

1) Cardiovascular

Ventricular tachycardia (including torsades de pointes) (5% > ≥0.1%), ventricular fibrillation (<0.1%), atrial flutter (5% > ≥0.1%), severe atrioventricular block (5% > ≥0.1%), transient cardiac arrest (<0.1%), sinus arrest (or sinoatrial block) (5% > ≥0.1%), aggravation of heart failure (5% > ≥0.1%) or Adams-Stokes syndrome (<0.1%) may occur. If any of these conditions occur, TAMBOCOR should be discontinued and the following measures considered (See “Overdosage” section.).

- i) Removal of unabsorbed drug from the gastrointestinal tract
- ii) Administration of cardiotonics, such as dopamine, dobutamine or isoprenaline, etc.
- iii) Assisted circulation such as IABP.
- iv) Pacing or electric defibrillation

2) Hepatic function disorders and jaundice

Hepatic function disorders (incidence unknown) and jaundice (incidence unknown) accompanied by elevation of AST (GOT), ALT (GPT) and γ -GTP may occur. The patient should be carefully observed. In the event of such symptoms, appropriate measures such as the discontinuation of TAMBOCOR, should be taken.

(2) Other adverse reactions

	5% > $\geq 0.1\%$	<0.1%
Cardiovascular ^{note1)}	Prolongation of PQ interval, QRS widening, polongation of QT, chest discomfort, palpitation, other forms of bradycardia, atrial fibrillation, increased blood pressure and edema	Other forms of bradycardia, decreased blood pressure, increased blood pressure, atrial fibrillation and chest pain
Psychoneurologic	Dizziness, light-headedness, headache, dull headache, tremor, drowsiness and numbness of hands and feet	Tinnitus
Gastrointestinal	Nausea, vomiting, abdominal pain, feeling of enlarged abdomen, thirst, anorexia, diarrhea, constipation, and dyspepsia	Stomatitis
Respiratory	Dyspnea	
Visual	Diplopia, photophobia and abnormal vision	Blurred vision
Hepatic	Elevation of AST(GOT), ALT(GPT), γ -GTP, Al-P, LDH and total bilirubin, etc.	
Renal	Elevation of BUN and serum creatinine, etc.	
Hypersensitivity ^{note2)}	Itching and rash	
Hematologic	Leucocytosis, and increase in hemoglobin and hematocrit	
Others	Malaise, numbness in the tongue, bitter taste / taste abnormality, facial flushing and diaphoresis	Micturition disorder such as pollakiuria, bitter taste, diaphoresis and taste abnormality

Note 1) The ECG should be monitored regularly and if any abnormal change is observed, treatment should be discontinued and appropriate measures taken.

- 2) In the event of such symptoms, treatment should be discontinued.

Incidences are calculated by combining the data from the clinical studies and post marketing surveillance.

5. Use in the Elderly

Since the elderly often have hepatic and renal hypofunction and tend to have a lower body weight, adverse reactions are liable to occur. Therefore, caution should be taken when administering TAMBOCOR to the elderly.

6. Use during Pregnancy, Delivery or Lactation

- (1) It should not be administered to pregnant women or women suspected of being pregnant.

[TAMBOCOR has been observed to have a teratogenic effect in animal experiments (in rats).]

- (2) The use of TAMBOCOR should be avoided during lactation. When TAMBOCOR must be used, breast feeding should be discontinued during treatment.

[In a human study it has been reported that TAMBOCOR is excreted in breast milk.]

7. Overdosage

- (1) Signs and Symptoms

Prolongation of ECG parameters, decrease in heart rate and myocardial contractility, conduction disturbance, life-threatening arrhythmia, convulsions, hypotension and death due to respiratory insufficiency, etc. caused by overdosage of TAMBOCOR have been reported.

- (2) Treatment

There is no specific antidote for TAMBOCOR overdosage at present. However, the following measures should be considered.

- 1) Removal of unabsorbed drug from the gastrointestinal tract
- 2) Administration of cardiotonics, such as dopamine, dobutamine or isoprenaline, etc.
- 3) Assisted circulation such as IABP
- 4) Pacing or electric defibrillation

Since the half-life of TAMBOCOR is long, it is necessary to continue the above measures as long as possible. It should be noted that hemodialysis is not effective.

8. Precautions concerning Use

Caution in handing over drug

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]

9. Other Precautions

The CAST clinical trial to determine efficacy in preventing sudden death was carried out on patients with asymptomatic ventricular extrasystole or non-sustained ventricular tachycardia after myocardial infarction. The mortality rate was reported to be higher for TAMBOCOR group than for the placebo group.¹⁾

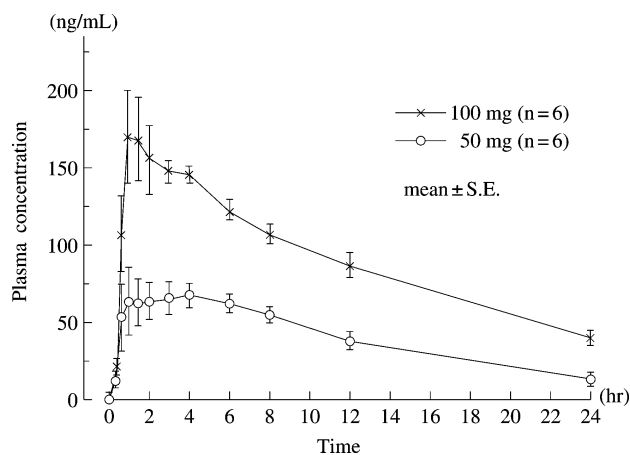
PHARMACOKINETICS

1. Blood concentration

(1) Blood concentration

When flecainide acetate is administered orally to 12 healthy adult male volunteers at single doses of 50 and 100 mg, it is well absorbed by the gastrointestinal tract. Plasma flecainide concentrations peak 2 to 3 hr after administration, with an elimination half-life of about 11 hr. Plasma concentrations increase near dose-dependently. A similar pharmacokinetic profile is obtained in patients with arrhythmia. When 50 or 100 mg of fle-

flecainide acetate is administered to 10 healthy adult male volunteers twice daily for seven consecutive days, plasma flecainide concentrations are steady after 4 days. The peak plasma flecainide concentrations are about twice that reached after the initial dose.^{2,3)}



Change in plasma flecainide concentration after single oral administration of flecainide acetate

Pharmacokinetic parameters after single oral administration of flecainide acetate

Dosage	Distribution volume (L/kg)	CL (mL/min/kg)	t _{1/2} (hr)	AUC _{0→∞} (ng · hr/mL)	C _{max} (ng/mL)
50mg	10.1±0.78	11.2±1.21	10.8±0.96	1,253±176.3	95±13.5
100mg	9.4±0.34	10.2±1.16	11.0±0.78	2,843±234.6	202±9.6

(Mean±S.E., n=6)

(2) Blood concentration after discontinuation of breast milk ingestion

When 25 mg of flecainide acetate was administered to an infant with paroxysmal supraventricular tachycardia every 6 hours orally (40 mg/kg/day ^{note}) and serum concentrations of flecainide acetate 2 hours after administration were compared for 2 cases: breast feeding and non-breast feeding. Serum concentrations were 990 ng/mL for the former and 1824 ng/mL for the latter.⁴⁾

Note) The dose of 40 mg/kg/day is not approved.

(3) Therapeutic drug monitoring (TDM)

Range of effective plasma concentration: 200 - 1,000 ng/mL

Frequency of determination : monthly

Main cytochrome P450 subfamily involved in metabolism : CYP2D6

2. Metabolism

The main metabolites of flecainide acetate are the meta-O-dealkylated form of flecainide and its glucuronide. Another metabolite is the oxidative lactam form of the piperidine ring. CYP2D6 of cytochrome P450 subfamily is mainly involved in O-dealkylation.⁵⁾

3. Excretion

When flecainide acetate is administered orally to healthy adult volunteers in a single dose, the urinary excretion rate

of unchanged drug within 24 hr after administration accounts for about 30% of the administered dose.²⁾

In a pharmacokinetic study conducted outside of Japan, about 86% (about 40% as flecainide) of the administered radioactivity had been excreted in the urine and 5% of it excreted in the feces within 6 days after oral administration of ¹⁴C-flecainide acetate to healthy adult volunteers.⁵⁾

CLINICAL STUDIES

Clinical efficacy

- (1) A multicenter double-blind clinical trial was carried out on patients with paroxysmal atrial fibrillation/flutter, paroxysmal supraventricular tachycardia and ventricular extrasystole. The clinical usefulness of TAMBOCOR was demonstrated in this trial.^{6,7)}
- (2) The results of clinical studies, including a double-blind clinical trial, are summarized below.

Disease	cases	Global improvement rate(%)	
		Remarkably improved	Remarkably to moderately improved
Ventricular extrasystole	448	254 (56.7)	328 (73.2)
Ventricular tachycardia	59	29 (49.2)	45 (76.3)
Complication of ventricular and supraventricular arrhythmia	19	11 (57.9)	13 (68.4)
Total	526	294 (55.9)	386 (73.4)

The effect of TAMBOCOR was evaluated from the non-recurrence rate of paroxysmal atrial fibrillation/flutter in a 28 day periods using trans-telephonic electrocardiography. The non-recurrence rate of paroxysmal atrial fibrillation/flutter was 3.1% (1/32) for placebo, 9.4% (3/32) for 100mg/day of TAMBOCOR and 39.4% (13/33) for 200mg/day (double-blind comparative study).

TAMBOCOR is not shown to have a life-prolonging effect in these clinical studies. Therefore, it should be considered that TAMBOCOR is generally hazardous to patients with mildly symptomatic ventricular arrhythmia.

PHARMACOLOGY

1. Effect on experimental arrhythmia

- (1) Flecainide acetate administered orally or intravenously inhibits ventricular arrhythmia induced in mice and dogs (by chloroform, adrenaline, ouabain or coronary artery ligation).⁸⁻¹⁰⁾
- (2) Intravenous administration of flecainide acetate inhibits atrial arrhythmia induced by aconitine in dogs.^{8,11)}

2. Electrophysiological actions

- (1) Flecainide acetate reduces the maximum rate of depolarization velocity (V_{max}) and action potential amplitude in dog Purkinje's fibers and ventricular muscle without affecting membrane resting potential.¹²⁾
- (2) Flecainide acetate inhibits V_{max} in guinea pig atrial and ventricular muscle in proportion to the frequency of stimulation.¹³⁻¹⁴⁾
- (3) In dogs, flecainide acetate prolongs the effective refractory period in ventricular muscle and reduces it in Purkinje's fibers.¹²⁾

(4) Flecainide acetate delays intra-atrial conduction, His-Purkinje (H-V) conduction and intraventricular conduction in dogs.¹⁵⁾

3. Clinical electrophysiological actions

When flecainide acetate is administered orally to patients with arrhythmia at a dose of 250 mg^{note)}, it delays H-V conduction and prolongs the effective refractory period of ventricular muscle without affecting the sinus rhythm or the recovery times of sinus node block. It also inhibits retrograde accessory conduction and prolongs the effective refractory period of the ventriculoatrial conduction system.¹⁶⁾

Note) Single dose of 250 mg is unapproved.

PHYSICOCHEMISTRY

Nonproprietary name: Flecainide Acetate (JAN)
Flecainide (INN)

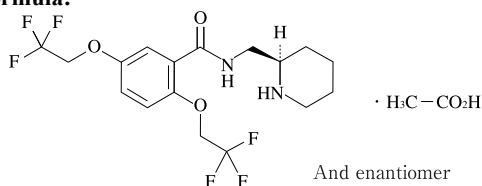
Chemical name:

N-[(2*RS*)-Piperidin-2-ylmethyl]-2,5-bis(2,2,2-trifluoroethoxy) benzamide monoacetate

Molecular formula: C₁₇H₂₀F₆N₂O₃ · C₂H₄O₂

Molecular weight: 474.39

Structural formula:



Description:

Flecainide acetate occurs as a white crystalline powder. It has a faint characteristic odor or a faint odor like that of acetic acid. It is freely soluble in methanol, in ethanol (95) and in acetic acid (100), sparingly soluble in water.

It shows no optical rotation.

Melting point: about 150°C (decomposition)

Partition coefficient: 0.34 (water: 1-octanol)

PACKAGING

Flecainide acetate Tablets, JP

TAMBOCOR Tablets 50 mg

Boxes of 100 and 500 in press-through packages, and bottles of 500

TAMBOCOR Tablets 100 mg

Boxes of 100 and 500 in press-through packages

REFERENCES

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REQUESTS FOR LITERATURE AND PRODUCT INFORMATION SHOULD BE MADE TO:

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