AUSTRALIAN PRODUCT INFORMATION

FLECATAB

(flecainide acetate) tablets

1 NAME OF THE MEDICINE

Flecainide acetate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each FLECATAB tablet contains 50 mg or 100 mg of flecainide acetate.

Excipients with known effect: contains trace amounts of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

FLECATAB (flecainide acetate) 50 mg tablet: normal convex white tablets debossed "FC" over "50" on one side and "G" on the other.

FLECATAB (flecainide acetate) 100 mg tablet: normal convex white tablet, debossed "FC/100" on one side and "G" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Flecainide is indicated for

1. Supraventricular arrhythmias,

   - due to pre-excitation syndromes (e.g. Wolff-Parkinson-White and Lown-Ganong-Levine syndromes)
   - due to dual atrioventricular (AV) nodal pathways in patients with debilitating symptoms
   - paroxysmal atrial flutter/fibrillation (PAF) associated with disabling symptoms

   Although flecainide acetate may be effective in supraventricular arrhythmias in patients with structural heart disease, its use has been associated with life-threatening and occasionally fatal ventricular arrhythmias. In these patients, particularly in the presence of impaired left ventricular function, FLECATAB should be used with extreme caution, preferably after other antiarrhythmic drugs have been tried or considered inappropriate.

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

2. Life-threatening ventricular arrhythmias not controlled by other drugs.

   An intravenous form of flecainide acetate is indicated when rapid control or short-term prophylaxis of the above arrhythmias is the main clinical requirement. All use of the injection (available in other brands) should be in hospitals only.

   FLECATAB is used for continuous maintenance of normal rhythm following initial oral or intravenous therapy or conversion by other means.

   Prescribers should also consult Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE of this Product Information.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

Adults

The dosage of flecainide acetate must be adjusted to the individual needs of each patient, based on therapeutic response and tolerance. The following regimen is suggested as a guideline. However, dosage may need to be adjusted if the age, weight or clinical status of the patient dictates.

When transferring patients who have been receiving another antiarrhythmic drug to FLECATAB, it is suggested that at least two plasma half-lives of the drug being discontinued should be allowed to elapse before starting FLECATAB at the usual dosage. In patients in whom withdrawal of a previous antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalising the patient.

In patients with supraventricular arrhythmias, treatment with FLECATAB, may be started on an outpatient basis, however in patients with sustained ventricular arrhythmias FLECATAB therapy should be initiated in hospital.

An intravenous form of flecainide acetate is indicated when rapid control or short-term prophylaxis of the above arrhythmias is the main clinical requirement. All use of the injection should be in hospitals only.

Flecainide acetate has a long half-life (12 to 27 hours in patients). Steady state plasma levels in patients with normal renal and hepatic function may not be achieved until the patient has received three to five days of treatment at a given dose. Therefore, increases in dosage should be made no more frequently than once every four days, since during the first two to three days of treatment the optimal effect of a given dose may not be achieved.

For patients with supraventricular arrhythmias (paroxysmal supraventricular tachycardia or paroxysmal atrial fibrillation/flutter), the recommended starting dose is 50 mg every twelve hours. The dose may be increased in increments of 50 mg twice daily every four days until efficacy is achieved. For patients with paroxysmal atrial fibrillation/flutter, a substantial increase in efficacy without a substantial increase in discontinuations for adverse experiences may be achieved by increasing the dose from 50 to 100 mg twice daily. The maximum recommended dose for patients with paroxysmal supraventricular arrhythmias is 300 mg/day.

For sustained ventricular tachycardia the recommended starting dose is 100 mg every twelve hours. This dose may be increased in increments of 50 mg twice daily every four days until efficacy is achieved. Most patients with sustained ventricular tachycardia do not require more than 150 mg every twelve hours (300 mg/day) and the maximum dose recommended is 400 mg/day.

An occasional patient not adequately controlled by or intolerant to a dose given every twelve hours may be given FLECATAB every eight hours.

Once adequate control of the arrhythmia has been achieved, the dosage may be lowered as necessary to reduce side effects or to minimise flecainide acetate's effects on conduction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). A loading dose to achieve more rapid control of the arrhythmia is not recommended because of the possibility that the use of a loading dose may increase the likelihood of adverse effects.

FLECATAB should be used cautiously in patients with a history of myocardial dysfunction or congestive heart failure.

In patients with severe renal impairment (creatinine clearance of 20 mL/minute/m^2 or less), the initial dosage should be 100 mg once daily (or 50 mg twice daily); when used in such patients, frequent plasma level monitoring is required to guide dosage adjustments. In patients with less severe renal disease, the initial dosage should be 100 mg every twelve hours; plasma level monitoring may also be useful in these patients during dosage adjustment. In both groups of patient’s dosage increases should be made very cautiously, monitoring the patient closely for signs of adverse cardiac effects or other toxicity.

It should be borne in mind that in these patients it may take longer than four days before a new steady state plasma level is reached following a dosage change.

In the presence of alkaline urine (pH > 7) dosage may need to be reduced (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Amiodarone

As for many other antiarrhythmic agents, in the presence of amiodarone, plasma levels of flecainide acetate may be altered. Four situations may be encountered.

1. FLECATAB stopped and amiodarone started: wait three plasma half-lives of flecainide acetate (about three days) before starting amiodarone.

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

3. Amiodarone stopped and FLECATAB started: as the elimination of amiodarone is extremely slow, FLECATAB should be started at a dose of 50 mg twice daily. Plasma level monitoring of flecainide acetate should be performed frequently. Based on therapeutic response and plasma flecainide acetate levels, the dosage of FLECATAB can be adjusted accordingly.

4. Amiodarone continued and FLECATAB started: when adding FLECATAB to the treatment regimen of a patient on a stabilised and well tolerated dose of amiodarone, FLECATAB should be commenced at a dose of 50 mg twice daily and plasma level monitoring of flecainide acetate should be performed frequently. Based on therapeutic response and plasma flecainide acetate levels, the dosage of FLECATAB can be adjusted accordingly. Dosage increase of FLECATAB should be made carefully in increments no more than 50 mg twice daily and only after levels of flecainide acetate have been obtained. If the dosage of amiodarone is changed, again carefully monitor plasma levels of flecainide acetate and adjust FLECATAB dosage accordingly.

Paediatric Use

Not recommended for use in children, as safety and efficacy have not been established.

Use in the Elderly

The rate of flecainide acetate elimination may be reduced in the elderly. An initial dose of 100 mg twice daily is recommended in otherwise healthy patients, with cautious increases in dosage.

Dosage adjustment in:

Renal Impairment

In patients with severe renal impairment, the dose of FLECATAB should be reduced (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION -Adult dosage, above). Plasma flecainide acetate should be monitored.

Plasma level monitoring.

The large majority of patients successfully treated with flecainide acetate were found to have trough plasma flecainide acetate levels varying between 200 and 1,000 nanogram/mL. The probability of cardiac adverse experiences may increase with higher trough plasma flecainide acetate levels, particularly when these exceed 1,000 nanogram/mL. Periodic monitoring of trough plasma flecainide acetate levels may be helpful to show whether a patient has received an adequate dose to obtain a plasma flecainide acetate level within the therapeutic range, or whether a patient has exceeded this range. Because elimination of flecainide acetate from plasma may be slower in patients with severe chronic renal failure or severe congestive heart failure, plasma flecainide acetate level monitoring may be especially important in these patients.

Hepatic Impairment

As flecainide acetate is extensively metabolised, presumably in the liver, patients with impaired hepatic function may require dosage adjustment and should be carefully monitored. Efficacy studies revealed sporadic elevation of serum alkaline phosphatase and transaminases but no studies in patients with hepatic impairment have been completed. Plasma level monitoring of flecainide acetate should be performed.

4.3 CONTRAINDICATIONS

1. Second or third degree atrioventricular (AV) block, except when a pacemaker is present to sustain rhythm.

2. Right bundle branch block when associated with a left hemiblock (bifascicular block) except when a pacemaker is present to sustain rhythm.

3. Cardiogenic shock.

4. Asymptomatic premature ventricular contractions and/or asymptomatic nonsustained ventricular tachycardia in patients with a history of myocardial infarction.

5. Known hypersensitivity to the drug.

6. Severe renal or hepatic impairment unless plasma level monitoring can be performed.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Mortality

In the Cardiac Arrhythmia Suppression Trial (CAST), a long-term, large scale, multicentre, double blind, randomised, placebo controlled clinical trial in patients with asymptomatic nonlife-threatening ventricular arrhythmia who had myocardial infarction more than 6 days but less than 2 years previously, oral flecainide acetate was associated with a higher incidence of mortality or nonfatal cardiac arrest (19/323) as compared with its matching placebo (7/318). The average duration of treatment with flecainide acetate in this study was 10 months. In that same study, an even higher incidence of mortality was seen in flecainide acetate 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 performed to determine if flecainide acetate is associated with a higher risk of mortality in other patient groups.

Structural Heart Disease

Patients with structural heart disease treated with flecainide acetate for supraventricular arrhythmias may be at increased risk for proarrhythmia and cardiac adverse events. Life-threatening and occasionally fatal ventricular arrhythmias have been associated with the use of flecainide acetate in these patients. Therefore, in these patients, particularly in the presence of impaired left ventricular function with ejection fraction ≤ 40%, flecainide acetate 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 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.

FLECATAB IS NOT RECOMMENDED FOR USE IN PATIENTS WITH CHRONIC ATRIAL FIBRILLATION.

Increased premature ventricular contractions (PVCs), ventricular tachycardia (VT), ventricular fibrillation (VF) and death were amongst the case reports of ventricular proarrhythmic effects in patients treated with flecainide acetate for atrial fibrillation/flutter.

As with other class I agents, patients treated with flecainide acetate 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 flecainide acetate. Concomitant negative chronotropic therapy (e.g. beta-blockers or digoxin) may reduce the risk of this complication.

Proarrhythmic Effects

As with other antiarrhythmic drugs, flecainide acetate 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. Flecainide acetate has been associated with episodes of unresuscitable ventricular tachycardia or ventricular fibrillation in a few patients. 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. In patients treated for recurrent sustained ventricular tachycardia, particularly those with congestive heart failure or low ejection fractions, treatment with any antiarrhythmic agent should be initiated in hospital. Effective use of flecainide acetate may be assisted in some patients by electrophysiological investigation.

Heart Failure

Because flecainide acetate 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%. FLECATAB should therefore be used cautiously in patients who are with a known history of congestive heart failure or myocardial dysfunction. The initial dose should be no more than 100 mg twice daily (see Section 4.2 DOSE AND METHOD OF 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 treatment with flecainide acetate, the onset has ranged from a few hours to several months after commencement of therapy. Some patients who develop evidence of decreased myocardial function while on FLECATAB can continue on FLECATAB with adjustment of digitalis or diuretic; others may require dosage reduction or discontinuation of FLECATAB. When feasible, it is recommended that plasma flecainide acetate levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 microgram/mL.

Effects on Cardiac Conduction

Flecainide acetate 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 flecainide acetate 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 0.2 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 by about 4%).

Although clinically significant conduction changes such as sinus pause, sinus arrest, and second or third degree atrioventricular block occasionally occur, an attempt should be made to reduce the dosage of flecainide acetate (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION) to the lowest effective dose in an effort to minimise these effects. If second or third degree atrioventricular block or right bundle branch block associated with a left hemiblock occurs, treatment with flecainide acetate should be discontinued unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker.

Sick Sinus Syndrome (bradycardia-tachycardia syndrome)

FLECATAB 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

Flecainide acetate 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS); 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 FLECATAB.

Effects on Pacemaker Thresholds

Flecainide acetate 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 initiating therapy with flecainide acetate, again after one week of administration and at regular intervals thereafter. Generally, threshold changes are within the range of multiprogrammable 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 flecainide acetate and other antiarrhythmic agents is not recommended.

Both disopyramide and verapamil have negative inotropic properties and the effects of concomitant use with flecainide acetate are unknown. Neither disopyramide nor verapamil should be given concurrently with FLECATAB unless, in the judgment of the physician, the benefit of this combination outweighs the risk.

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

Lidocaine has been used occasionally with flecainide acetate while awaiting the therapeutic effect of flecainide acetate. 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 > 7), which may result from diet, concomitant medication or disease states, flecainide acetate elimination may be slower, as has also been reported for other basic compounds, and flecainide acetate dosage may need to be reduced.

Blood Dyscrasias

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

Use in Renal Impairment

A reduced dosage is recommended in cases of severe renal impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Renal Impairment**)**. Haemodialysis is ineffective in removing unchanged flecainide acetate from the body.

Use in Hepatic Impairment

Flecainide acetate is not recommended in patients with significant hepatic impairment unless potential benefits outweigh risk. (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Hepatic Impairment)

Use in the Elderly

See Section 4.4 DOSE AND METHOD OF ADMINISTRATION – Use in the Elderly.

Paediatric Use

See Section 4.4 DOSE AND METHOD OF ADMINISTRATIONON – Paediatric Use.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alcohol

There is no information available.

Food

The rate and extent of flecainide acetate absorption is not affected by food.

Drugs

Digoxin

During multiple oral dosage of flecainide acetate 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. Flecainide acetate has been administered to patients receiving digitalis preparations without adverse effects.

Beta-adrenergic blocking agents

Flecainide acetate has been administered to patients receiving beta-blockers without adverse effects. In a formal interaction study conducted in healthy males receiving flecainide acetate and propranolol concomitantly, plasma flecainide acetate levels were about 20% higher and propranolol levels were about 30% higher, in comparison to control values. These small changes should be of no clinical consequence. In this study flecainide acetate 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 concurrent administration of flecainide acetate and propranolol on the PR interval were less than additive. While these effects were of little clinical consequence in the healthy subjects, the possibility of exaggerated effects from this combination in patients with reduced left ventricular function should be borne in mind. In flecainide acetate clinical trials, patients who were receiving beta-adrenergic blocking agents concomitantly did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta-blockers and flecainide acetate should be recognised.

Antiarrhythmics

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE– Concommitant Antiarrythmic Therapy.

Nifedipine, diltiazem

There has been too little experience with the co-administration of flecainide acetate and nifedipine or diltiazem to recommend concomitant use.

Diuretics

Flecainide acetate 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 acetate levels increased by about 30% and half-life increased by about 10%.

Other drugs

Although formal interaction studies have not been conducted with flecainide acetate and other drugs, flecainide acetate is not extensively bound to plasma proteins and, consequently, interactions with other drugs that 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 elimination of flecainide acetate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Flecainide acetate 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, FLECATAB 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 flecainide acetate during labour or delivery has immediate or delayed adverse effects on the mother or foetus, or whether it affects the duration of labour or delivery, or increases the possibility of forceps delivery or other obstetric intervention.

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since flecainide acetate can cause light headedness, dizziness, faintness and visual disturbance, patients should be cautioned about engaging in activities requiring judgment and physical coordination (e.g. driving a vehicle or operating dangerous machinery) when these effects occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Flecainide acetate 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 flecainide acetate 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, flecainide acetate therapy has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second (0.5%) or third (0.4%) degree atrioventricular block. A total of 1.2% of patients developed sinus bradycardia, sinus pause or sinus arrest (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The frequency of most of these serious adverse reactions probably increases with higher trough plasma levels, particularly when these trough levels exceed 1.0 microgram/mL.

The most commonly reported non-cardiac reactions experienced by patients with ventricular arrhythmias were dizziness 27%, visual disturbance 26% (including blurred vision, diplopia, visual field defects, photophobia), headache 10%, nausea 10% and dyspnoea 9%.

Other adverse reactions occurring in over 3% of the patients in clinical trials included the following.

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%.

Dermatological. Rash 4%.

The following additional adverse reactions, possibly related to flecainide acetate treatment and occurring in 1 to < 3% of patients, have been reported in clinical trials.

Body as a whole. Pain, increased sweating, flushing, dry mouth, arthralgia, fever, myalgia.

Cardiovascular. Oedema, syncope, tachycardia, angina pectoris, conduction disturbance.

Gastrointestinal. Vomiting, diarrhoea, anorexia.

Central nervous system. Hypoaesthesia, somnolence, insomnia, ataxia.

Respiratory. Coughing.

Dermatological. Pruritus.

Special senses. Tinnitus.

Genitourinary. Micturition disorder (including urinary retention, frequency, polyuria, dysuria).

The following additional adverse experiences, possibly related to flecainide acetate, have been reported in < 1% of patients.

Body as a whole. Impotence, decreased libido, gynaecomastia, malaise.

Cardiovascular. Bradycardia, ECG abnormality, hypertension, hypotension, heart disorder, myocardial infarction, peripheral ischaemia, pulmonary oedema.

Gastrointestinal. Dyspepsia, flatulence, gastrointestinal haemorrhage.

Central nervous system. Anxiety, twitching, convulsions, nystagmus, stupor, dysphonia, speech disorder, coma, amnesia, confusion, depersonalisation, hallucination, paranoid reaction, euphoria, apathy.

Respiratory. Bronchospasm, laryngismus.

Dermatological. Dermatitis, hypertrichosis, photosensitivity reaction, skin discolouration.

Special senses. Deafness, parosmia, loss of taste, taste perversion.

Genitourinary. Renal failure, haematuria.

Laboratory abnormalities. Hyperglycaemia, increased nonprotein nitrogen, increased serum alkaline phosphatase, increased serum ALT and AST. Patients with elevations of liver function tests have been asymptomatic and no cause and effect relationship with flecainide acetate has been established.

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

Flecainide acetate has been evaluated in 225 patients with supraventricular arrhythmias. The most serious adverse reactions reported for flecainide acetate in patients with supraventricular arrhythmias were new or worsened supraventricular or ventricular arrhythmias, which were reported in 4% of patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), 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 noncardiac adverse reactions for supraventricular arrhythmia patients remain consistent with those known for patients treated with flecainide acetate for ventricular arrhythmias. Reactions included 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 databases because many of the supraventricular arrhythmia patients were dosed to tolerance in the clinical trials.

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Although no cause and effect relationship has been established, it is advisable to discontinue flecainide acetate in these patients in order to eliminate flecainide acetate as the possible causative agent.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

No data are available concerning overdosage of flecainide acetate in humans. However, animal studies suggest the following events may occur: lengthening of the PR interval; increase 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.

Treatment

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 flecainide acetate (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 flecainide acetate from the body.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Flecainide acetate belongs generally to the membrane stabilising (Class I) group of antiarrhythmic agents; however, it has its own characteristic electrophysiological effects. Its predominant effect on the transmembrane action potential in single cell preparations from canine Purkinje fibres is to reduce the rate of rise (V_{max}, phase 0) of the action potential without greatly affecting duration. In these same preparations, the duration of the effective refractory period was lengthened and little, if any, change was observed in the slope of phase 4 depolarisation. In ventricular muscle, some lengthening of the action potential duration has been found. These results are consistent with the postulate that the predominant action of flecainide acetate is to inhibit the fast, or sodium, channel which is largely responsible for the rapid upstroke of the myocardial action potential in cardiac conducting tissue. No significant anticholinergic or alpha or beta antiadrenergic effects have been observed in animal studies. Animal studies have also shown that flecainide acetate possesses a significant degree of local anaesthetic activity.

<u>Electrophysiology.</u>

Studies of the effects of flecainide acetate on intracardiac conduction in humans have shown that the drug depresses conduction in all parts of the heart with the greatest effect on the His-Purkinje system (His-ventricular (H-V) conduction). Smaller increases were observed in atrioventricular nodal conduction and in intra-atrial conduction times, and effects on refractory periods were less pronounced than those on conduction velocity. Sinus node recovery times (corrected) following pacing and spontaneous cycle lengths were increased, but not significantly, in patients with normal sinus node function. Pronounced depression of sinus node function in patients with sinus node dysfunction has been reported. Significant prolongation of the PR interval, QRS duration and the QT interval (corrected) have been detected electrocardiographically in human studies, although the JT (QT minus QRS) interval is not significantly affected. Flecainide acetate is known to reversibly increase endocardial pacing thresholds.

Haemodynamics.

Flecainide acetate does not usually alter heart rate, although bradycardia and tachycardia have been reported infrequently. In clinical studies, mean systolic and diastolic blood pressures increased slightly and sometimes significantly during therapy.

Single dose oral and intravenous studies have provided evidence for a slight negative inotropic effect for flecainide acetate. Evidence for slightly but significantly reduced myocardial contractility with maintained pump function was detectable following administration of a single 250 mg oral dose to patients and healthy subjects using systolic time intervals as well as M-mode and two dimensional echocardiography. Patients with chronic stable ventricular arrhythmias without significant pre-existing congestive failure have shown no changes in ejection fraction and other indices of contractility as determined by echocardiography after two weeks of treatment with therapeutic doses of flecainide acetate. One study of patients with complex ventricular arrhythmias having a mean pre-flecainide ejection fraction of about 42% showed a slight but significant decrease to 38% in this parameter after short-term therapy. Another study of patients with ventricular tachycardia and a mean pre-treatment ejection fraction of 22% showed no change in ejection fraction after 4 to 14 days of flecainide acetate therapy (mean daily dose 242 mg).

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absorption of oral flecainide acetate is reasonably prompt and nearly complete. In most individuals, peak plasma drug levels are reached at about three hours (range one to six hours). Therapeutic plasma levels of flecainide acetate range from 0.2 to 1.0 microgram/mL. Flecainide acetate does not undergo any first-pass metabolism. Food does not affect either the rate or the extent of absorption of flecainide acetate. The mean plasma half-life in patients with premature ventricular contractions following multiple oral dosage is about 20 hours (range 12 to 27 hours). The volume of distribution ranges from 5 to 13.4 L/kg (mean 8.7 L/kg) indicating that flecainide acetate is widely distributed into the tissues.

Distribution

Flecainide acetate is about 40% bound to human plasma proteins and the extent of protein binding is independent of plasma drug concentration over the range 15 to 3,400 nanogram/mL.

Metabolism

Metabolic degradation of flecainide acetate appears to be genetically determined. Poor metabolisers have lower metabolic clearance of flecainide acetate. However, since flecainide acetate, to a large extent, is also excreted renally, it is unlikely that a reduced metabolic clearance in poor metabolisers is of any clinical consequence, except in patients with renal failure.

Excretion

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, *m*-O-dealkylated flecainide and the *m*-O-dealkylated lactam of flecainide in conjugated and unconjugated forms account for most of the remaining portion of the dose.

For patients with moderate renal failure, the rate of elimination of flecainide acetate from plasma and the extent of unchanged drug excretion in urine are only somewhat less than for healthy subjects. In contrast, in patients with endstage renal disease, the extent of flecainide acetate excretion in urine is markedly lower. The rate of elimination of flecainide acetate from plasma is also slower in some endstage patients. In patients with congestive heart failure (New York Heart Association (NYHA) class III), the rate of flecainide acetate elimination from plasma is about 25% slower than for healthy subjects, but the extent of unchanged drug excretion in urine is comparable. (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION for dosage in patients with renal disease or congestive heart failure.)

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following inactive excipients: croscarmellose sodium, microcrystalline cellulose and magnesium stearate. *The tablets are gluten free.*

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al

Pack sizes: 60

Australian Register of Therapeutic Goods (ARTG)

AUST R 344750 – FLECATAB flecainide acetate 50 mg tablet blister pack

AUST R 68651 – FLECATAB flecainide acetate 100mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

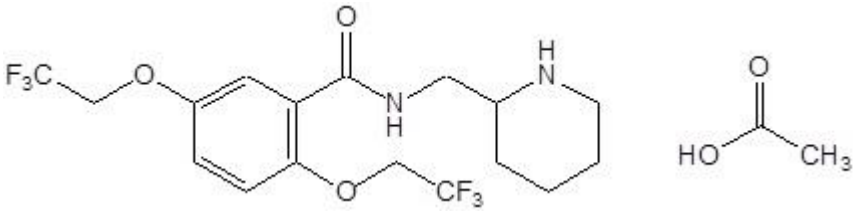
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Flecainide acetate belongs to the benzamide class of antiarrhythmic drugs and is structurally related to lidocaine and procainamide. It is chemically distinguished from these agents by the presence of trifluoroethoxy substituents in the aromatic portion of the molecule and a piperidine ring in the amide side chain instead of the diethylaminoethyl group of the procainamide side chain. The compound is a racemic mixture.

Flecainide acetate is soluble in water, dilute acetic acid, methanol and ethanol, and practically insoluble in dilute hydrochloric acid.

Chemical Structure



Chemical name

N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide acetate

Molecular formula

$C_{17}H_{20}F_6N_2O_3$, $C_2H_4O_2$

CAS Number

The Chemical Abstracts Service (CAS) Registry Number of the medicine.

CAS Registry no. 54143-56-5

Molecular weight:

474.4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

FLECATAB flecainide acetate 100mg tablet blister pack: 26/08/1999

FLECATAB flecainide acetate 50 mg tablet blister pack: 1/09/2021

10 DATE OF REVISION

11/12/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial updates throughout
2.	Excipients with known effect added

FLECATAB_pi\Dec23/00