

New Zealand Data Sheet

1 FLECAINIDE BNM

FLECAINIDE BNM 50 mg and 100 mg tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Flecainide acetate 50 mg

Each tablet contains flecainide acetate 50 mg.

Flecainide acetate 100 mg

Each tablet contains flecainide acetate 100 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Flecainide 50 mg tablets: White, circular, biconvex, uncoated tablets embossed “C” on one face and the identifying letters “FI” on the reverse.

Flecainide 100 mg tablets: White, circular, biconvex, uncoated tablets embossed with a break line on one face with the identifying letters “C” above the line and “FJ” below, the reverse with a break line. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In patients without structural heart disease and without myocardial infarction, Flecainide BNM tablets are indicated for the prevention of:

Supraventricular arrhythmias

- paroxysmal supraventricular tachycardias (PSVT) including atrioventricular nodal reentrant tachycardia, atrioventricular reentrant 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 flecainide in chronic atrial fibrillation has not been adequately studied and is not recommended.

4.2 Dose and method of 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.
- Flecainide can increase pacing or defibrillation thresholds, so this should be considered when electrical devices such as pacemakers and defibrillators are used.
- Because flecainide 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 blood levels and necessitate special caution in dosing. The long half-life of flecainide along with the absence of a satisfactory method to remove the medicine encourages one to begin dosing carefully and avoid overload with the medicine.
- It should also be noted that amiodarone may increase plasma flecainide concentrations.
- Treatment with Flecainide BNM should be monitored by frequent ECG recordings and/or plasma level monitoring as recommended.

Dose

For patients with paroxysmal supraventricular arrhythmias, Flecainide BNM 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 twice daily 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.

For patients with symptomatic sustained ventricular arrhythmias, Flecainide BNM 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 twice daily at intervals of at least four days until efficacy is achieved. The maximum recommended dose is 400 mg/day and this is normally reserved for patients of large build or where rapid control of the arrhythmia is required.

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. Flecainide BNM stopped and amiodarone started. Wait three plasma half-lives of flecainide (about 3 days) before starting amiodarone.
2. Flecainide BNM continued and amiodarone introduced. The dose of Flecainide BNM 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, Flecainide BNM 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 Flecainide BNM started. As the elimination of amiodarone is extremely slow, Flecainide BNM should be started at a dose of 50 mg twice daily. Plasma level monitoring of flecainide should be done frequently. Based on therapeutic response and plasma levels the dosage of Flecainide BNM can be adjusted accordingly.
4. Amiodarone continued and Flecainide BNM started. When adding Flecainide BNM to the regimen of a patient on a stabilised and well tolerated dose of amiodarone, Flecainide BNM should be started at a dose of 50 mg twice daily and plasma level monitoring of flecainide should be done frequently. Based on therapeutic response and plasma levels, the dosage of Flecainide BNM can be adjusted accordingly. Increases in Flecainide BNM dosage should be made carefully in increments not exceeding 50 mg twice daily 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 Flecainide BNM dosage accordingly.

Structural heart disease

Use of Flecainide BNM 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 Flecainide BNM. This applies to the initiation of therapy, changes in dosage and control of long term therapy with Flecainide BNM. ECG monitoring should be performed at 2 to 4 day intervals at the beginning of therapy, and particularly following dose increases. Monitoring of ECG is recommended at regular intervals during therapy – ECG control once a month and long term ECG every 3 months.

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 Flecainide BNM 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 Flecainide BNM.

When flecainide is used in patients with dosage restrictions, frequent ECG control (additional to the regular flecainide plasma monitoring) should be made. Dose adjustment should be made at intervals of 6-8 days. In such patients an ECG should be performed in weeks 2 and 3 to control the individual dosage.

Plasma level monitoring

Periodic monitoring of trough plasma levels may be useful in patient management. The large majority of patients successfully treated with flecainide 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. 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.

Special populations

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. In elderly patients the maximum initial daily dosage should be 50 mg twice daily as the rate of flecainide elimination from plasma may be reduced in elderly people. This should be taken into consideration when making dose adjustments. The dose for elderly patients should not exceed 300 mg daily (or 150 mg twice daily).

Renal impairment

In patients with significant renal impairment (creatinine clearance of ≤ 35 mL/min/ 1.73 m² or serum creatinine > 1.5 mg/dL) the maximum initial dosage should be 100 mg daily (or 50 mg twice daily). When used in such patients, frequent plasma level monitoring is strongly recommended. Depending on the effect and tolerability the dose may then be cautiously increased. After 6-7 days the dose may be adjusted, depending on the effect and the tolerability. Some patients with severe renal failure can have a very slow clearance

of flecainide and thus a prolonged half-life (60-70 hours).

Hepatic impairment

In patients with impaired liver function, the patient should be closely monitored and the dose should not exceed 100 mg daily (or 50 mg twice daily).

Patients with a permanent pacemaker in situ should be treated with caution and the dose should not exceed 100 mg twice daily since flecainide is known to increase endocardial pacing thresholds.

In patients concurrently receiving cimetidine or amiodarone close monitoring is required. In some patients the dose may have to be reduced and should not exceed 100 mg twice daily. Patients should be monitored during initial and maintenance therapy.

Paediatric population

Flecainide BNM 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 flecainide in children of varying ages with supraventricular tachycardia but with structurally normal hearts. Similar empirical evidence of effectiveness exists for the use of flecainide 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 flecainide 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.

Method of administration

Flecainide BNM tablets are for oral administration

4.3 Contraindications

- Known hypersensitivity to flecainide or to any of the excipients (see section 6.1 for list of excipients)
- Structural heart disease
- Haemodynamically significant valvular heart disease
- Unless pacing rescue is available, flecainide must not be given to patients with sinus node dysfunction, atrial conduction defects, second degree or greater atrio-ventricular block, bundle branch block or distal block
- 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.
- Reduced or impaired ventricular function, cardiogenic shock, severe bradycardia (less than 50 bpm), severe hypotension
- Asymptomatic or mildly symptomatic ventricular arrhythmias.
- Post-myocardial infarction patients
- Cardiac failure

- Long standing atrial fibrillation in whom there has been no attempt to convert to sinus rhythm
- Use in combination with class I antiarrhythmics (sodium channel blockers)
- Significant renal or hepatic impairment, unless potential benefits outweigh risks. If used, frequent plasma level monitoring is required to guide dosage.

4.4 Special warnings and precautions for use

Initiation of flecainide acetate therapy and dose changes should be made in hospital under ECG and plasma level monitoring.

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 medicines 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 flecainide for supraventricular arrhythmias, may be at increased risk for proarrhythmia and cardiac adverse events. The use of flecainide 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 $\leq 40\%$, Flecainide BNM should be used with extreme caution, preferably after other antiarrhythmic medicines 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.

FLECAINIDE IS NOT RECOMMENDED FOR USE IN PATIENTS WITH CHRONIC ATRIAL FIBRILLATION. Case reports of ventricular proarrhythmic effects in patients treated with flecainide 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 flecainide 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 BNM. Concomitant negative chronotropic therapy such as digoxin or β -blockers may lower the risk of this complication.

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

Proarrhythmic effects

As with other antiarrhythmic medicines flecainide 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 flecainide 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 Flecainide BNM may be assisted in some patients by electrophysiological investigation.

Heart failure

Because flecainide 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 $\leq 40\%$. Flecainide BNM 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 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 flecainide 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 flecainide can continue on Flecainide BNM with adjustment of digitalis or diuretic, others may require dosage reduction or discontinuation of Flecainide BNM. 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 $\mu\text{g/mL}$.

Effects on cardiac conduction

Flecainide 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 medicine 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%.)

Flecainide has a selective effect that increases the refractory period of the anterograde, and especially, the retrograde pathways. These effects are reflected in the ECG by prolongation of the QTc interval in most patients; consequently, there is little effect on the JT interval.

Nevertheless, there have been reports of prolongation of the JT interval of up to 4%. This action is less marked than that observed with the class 1a antiarrhythmic medicines however.

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 Flecainide BNM (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 AV block, or right bundle branch block associated with a left hemi-block occur, Flecainide BNM therapy should be discontinued unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker.

Sick sinus syndrome (bradycardia-tachycardia syndrome)

Flecainide BNM 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 BNM 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 Interaction with other medicines and other forms of interaction), 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 medicines. Any pre-existing hypokalaemia or hyperkalaemia or other electrolyte disturbances should be corrected before administration of Flecainide BNM. Hypokalaemia may occur in patients who use diuretics, corticosteroids or laxatives.

Effects on pacemaker thresholds

Flecainide 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 Flecainide BNM, 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 but it may be difficult to obtain ventricular thresholds less than 1 Volt at initial implantation in the

presence of flecainide.

Concomitant antiarrhythmic therapy

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

Both disopyramide and verapamil have negative inotropic properties and the effects of co-administration with flecainide are unknown. Neither disopyramide nor verapamil should be administered concurrently with Flecainide BNM, 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 flecainide. 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 Flecainide BNM is to be administered in the presence of amiodarone, the dose of Flecainide BNM should be reduced (see section 4.2 Dose and method of administration) with plasma flecainide monitoring.

Lidocaine has been used occasionally with flecainide while awaiting the therapeutic effect of flecainide. No adverse 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, flecainide elimination may be slower, as has also been reported for other basic compounds and Flecainide BNM dosage may need to be reduced.

Renal impairment

Renal impairment requires particular caution during treatment with Flecainide BNM.

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 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 Flecainide BNM 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 Flecainide BNM.

Since elimination of flecainide from plasma can be markedly slower in patients with significant hepatic impairment, treatment with Flecainide BNM 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.

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.

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 Flecainide BNM in patients who develop blood dyscrasias, in order to eliminate Flecainide BNM 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 BNM in patients who develop lung disease, in order to eliminate Flecainide BNM as the possible causative agent.

4.5 Interaction with other medicines and other forms of interaction

Alcohol

No information available.

Food

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

Medicines

Digoxin

During multiple oral dosage of flecainide 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 has been administered to patients receiving digitalis preparation without adverse effects. It is recommended that the digoxin plasma level in digitalised patients should be measured not less than 6 hours after any digoxin dose, before or after administration of flecainide.

β-adrenergic blocking agents

Flecainide has been administered to patients receiving β-adrenergic blocking agents without adverse effects. In a formal interaction study conducted in healthy males receiving flecainide and propranolol concurrently, plasma flecainide 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, flecainide 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 flecainide 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 clinical trials, patients who were receiving β-blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of β-blockers and flecainide should be recognised.

Anti-arrhythmics

See section 4.4 "Special **warnings and precautions for use – Concomitant antiarrhythmic therapy**".

Nifedipine, Diltiazem

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

Diuretics

Flecainide 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 flecainide and other medicines, flecainide is not extensively bound to plasma proteins and consequently interactions with other medicines that are highly protein bound (e.g. anticoagulants) would not be expected.

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, medicines that inhibit cytochrome P4502D6 might increase the plasma concentrations of flecainide during chronic therapy. Furthermore, flecainide is itself an inhibitor of cytochrome P4502D6 and may contribute to such increases in its own plasma levels.

Flecainide is metabolised by cytochrome P450 CYP2D6 to a large extent, and concurrent use of medicines that inhibit this iso-enzyme can lead to decreased elimination and increased plasma concentrations of flecainide. Medicines that induce cytochrome P450 can lead to decreased plasma concentrations of flecainide. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination.

When flecainide is given in the presence of amiodarone, the usual dosage should be reduced by 50% and the patient monitored closely for adverse effects. Since cimetidine and amiodarone are both strong inhibitors of CYP2D6, plasma level monitoring is strongly recommended in these circumstances.

Other possible medicine interactions with flecainide:

- paroxetine, fluoxetine and some other antidepressants inhibit CYP2D6 and therefore can increase the plasma level of flecainide
- terbinafine is known as a CYP2D6 inhibitor
- quinidine (class I anti-arrhythmic) increases the concentration of flecainide by inhibiting CYP2D6 and should not be co-prescribed

- astemizole and terfenadine (antihistamines) increase the risk of arrhythmias
- quinine and halofantrine (antimalarials)
- flecainide should not be used in combination with calcium antagonists such as verapamil
- ritonavir, lopinavar and indinavir (antivirals) can increase plasma concentration of flecainide
- diuretics e.g. thiazides and loop diuretics (bumetanide)
- bupropion (anti-smoking medicine).

Combination with these medicines should be avoided when possible, otherwise the patient has to be monitored closely and the flecainide dose may be reduced if needed.

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, Flecainide BNM should not be used during pregnancy unless as a medicine of last resort in life-threatening arrhythmias. If Flecainide BNM is used during pregnancy, maternal flecainide plasma levels should be monitored throughout pregnancy.

Labour and delivery

It is not known whether the use of flecainide 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

Breastfeeding

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

Fertility

No information held by the sponsor.

4.7 Effects on ability to drive and use machines

Since flecainide 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

Flecainide 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 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 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 "Special warnings and precautions **for use**"). 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 flecainide 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 – pruritis

Special Senses – tinnitus

Urinary System – micturition disorder (includes urinary retention, frequency, polyuria, dysuria).

The following additional adverse experiences, possibly related to flecainide, have been reported in less than 1% of patients:

Body as a Whole – impotence, decreased libido, gynaecomastia, malaise, vertigo

Cardiovascular – bradycardia, ECG 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 flecainide 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%.

Flecainide has been evaluated in 225 patients with **supraventricular arrhythmias**. The most serious adverse reactions reported for flecainide 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 non-cardiac adverse reactions for supraventricular arrhythmia patients remain consistent with those known for patients treated with flecainide 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.

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 Flecainide 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 flecainide 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 flecainide injection for conversion of acute arrhythmias. This effect is usually short lived

and abates quickly following cessation of therapy.

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 BNM in these patients in order to eliminate flecainide as the possible causative agent.

Further reports include the following:

Very common (>1/10)
 Common (>1/100, <1/10)
 Uncommon (>1/1 000, <1/100)
 Rare (>1/10 000, <1/1 000)
 Very rare (<1/10 000)

Immune system disorders

Very rare: a small number of cases of increases in anti-nuclear antibodies with and without systemic inflammatory involvement

Nervous system disorders

Common: dyskinesia
 Uncommon: peripheral neuropathy

Eye disorders

Very common: accommodation difficulties
 Very rare: corneal deposits

Skin and subcutaneous tissue disorders

Uncommon: alopecia and urticaria

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

Clinical features

No data are available concerning overdosage of flecainide 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.

Management

Overdose with flecainide is a potentially life threatening medical emergency. No specific antidote is known. If justified, measures to reduce absorption (gastric lavage or administration of activated charcoal) can be used.

Treatment of overdose should be supportive and may include the following: administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoprenaline, intravenous calcium, 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 (range from 12 to 27 hours in patients), these supportive treatments may need to be continued for extended periods of time.

There is no known way of rapidly removing flecainide from the system but forced acid diuresis may theoretically be helpful. Neither dialysis nor haemoperfusion are helpful and injections of anticholinergics are not recommended.

For the treatment of Flecainide BNM overdose when urine is clearly alkaline, acidification of urine (e.g. with ammonium chloride) may promote flecainide 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).

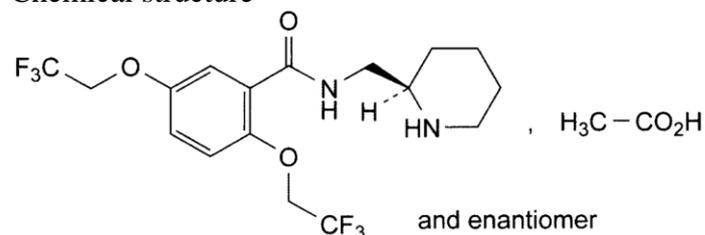
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics, class IC, Flecainide
ATC code: CO1 BC 04

Chemistry information

Chemical structure



Molecular formula: C₁₇H₂₀F₆N₂O₃, C₂H₄O₂

Molecular weight: 474.4

CAS number: 54143-56-5

Mechanism of action

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.

Flecainide 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.

Flecainide 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).

Flecainide 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.

Pharmacodynamic effects

Supraventricular arrhythmia

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

Ventricular arrhythmia

Flecainide 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

Absorption

Following oral administration, the absorption of flecainide from Flecainide BNM tablets is nearly complete. The bioavailability from flecainide acetate tablets has been reported to be about 90%.

Peak plasma levels are reached after about three hours in most individuals (range 1 to 6 hours). The therapeutic plasma concentration range is generally accepted as 200 to

1000 ng per mL. Flecainide does not undergo any consequential presystemic biotransformation (first-pass effect). Food or antacids do not affect absorption.

Distribution

Flecainide is about 40% bound to plasma proteins. Flecainide passes the placenta and is excreted in breast milk.

Biotransformation

Flecainide is extensively metabolised (subject to genetic polymorphism), the 2 major metabolites being m-O-dealkylated flecainide and m-O-dealkylated lactam of flecainide, both of which may have some activity. Its metabolism appears to involve the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism.

Elimination

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 medicine 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).

In healthy subjects, about 30% of a single oral dose (range 10 to 50%) is excreted in urine as unchanged medicine. 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 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 medicine 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.

5.3 Preclinical safety data

Refer to section 4.6 and 4.9 for relevant data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- croscarmellose sodium
- magnesium stearate
- starch – pregelatinised maize
- starch – maize
- cellulose – microcrystalline.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blister packs of 60 tablets

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Flecainide BNM 100 mg - 25 July 2013
Flecainide BNM 50 mg - 13 August 2015

10 DATE OF REVISION OF TEXT

23 May 2018

Summary table of changes

Section changed	Summary of new information
Full Datasheet	Datasheet format updated in line with the new Medsafe datasheet SPC format
Section 4.4	Cytochrome P450IID6 Metabolism precaution moved to section 4.5. Cytochrome P450IID6 changed to cytochrome P4502D6