For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

8037279-805

FLECARITE

(Flecainide Tablets B.P.)

Composition

FLECARITE 50

Each uncoated tablet contains :

Flecainide Acetate B.P. 50 mg

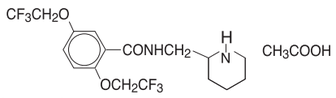
FLECARITE 100

Each uncoated tablet contains:

Flecainide Acetate B.P. 100 mg

Description

Flecainide acetate is N-[(RS)-(Piperidin-2-ylmethyl)]-2,5-bis(2,2,2-trifluoro ethoxy) benzamide acetate. It is white or almost white, very hygroscopic, crystalline power. It is soluble in water and in anhydrous ethanol. It is freely soluble in dilute acetic acid and practically insoluble in dilute hydrochloric acid. The molecular formula of Flecainide acetate is $C_{17}H_{20}F_6N_2O_3$. $C_2H_4O_2$ and its molecular weight is 474.4. The structural formula is given below:



Clinical Pharmacology

Pharmacodynamic

Flecainide slows conduction through the heart, having its greatest effect on His Bundle conduction. It also acts selectively to increase anterograde and particularly retrograde accessory pathway refractoriness. Its actions may be reflected in the ECG by prolongation of the PR interval and widening of the QRS complex. The effect on the JT interval is insignificant. Significant effects on refractory periods were observed only in the ventricle. 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.

Pharmacokinetic

Oral administration of flecainide results in extensive absorption, with bioavailability approaching 90 to 95%. Peak plasma levels are attained at about three hours in most individuals (range, 1 to 6 hours). Flecainide does not appear to undergo significant hepatic first-pass metabolism. In patients, 200 to 500 mg flecainide daily produced plasma concentrations within the therapeutic range of 200-1000 µg/L. Protein binding of flecainide is within the range 32 to 58%. Food or antacid do not affect absorption. Milk, however, may inhibit absorption in infants. A reduction in flecainide dosage should be considered when milk is removed from the diet of infants.

In vitro metabolic studies have confirmed that cytochrome P450IID6 is involved in the metabolism of flecainide.

Recovery of unchanged flecainide in urine of healthy subjects was approximately 42% of a 200mg oral dose, whilst the two major metabolites (Meta-O-Dealkylated and Dealkylated Lactam Metabolites) accounted for a further 14% each. The elimination half-life was 12 to 27 hours. When urinary pH is very alkaline (8 or higher), as may occur in rare conditions (e.g., renal tubular acidosis, strict vegetarian diet), flecainide elimination from plasma is much slower.

The elimination of flecainide from the body depends on renal function (i.e., 10 to 50% appears in urine as unchanged drug). With increasing renal impairment, the extent of unchanged drug excretion in urine is reduced and the plasma half-life of flecainide is prolonged. Since flecainide is also extensively metabolized, there is no simple relationship between creatinine clearance and the rate of flecainide elimination from plasma.

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

Indication

Flecainide tablets are indicated for:

a) AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways.

b) Paroxysmal atrial fibrillation in patients with disabling symptoms when treatment need has been established and in the absence of left ventricular dysfunction. Arrhythmias of recent onset will respond more readily.

c) Symptomatic sustained ventricular tachycardia.

d) Premature ventricular contractions and/or non-sustained ventricular tachycardia which are causing disabling symptoms, where these are resistant to other therapy or when other treatment has not been tolerated.

Flecainide tablets can be used for the maintenance of normal rhythm following conversion by other means.

Flecainide tablets are for oral administration

Contraindication

Flecainide is contra-indicated in cardiac failure and in patients with a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia. It is also contra-indicated in patients with long standing atrial fibrillation in whom there has been no attempt to convert to sinus rhythm, and in patients with haemodynamically significant valvular heart disease. Unless pacing rescue is available, Flecainide should 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. Flecainide is contra-indicated in case of hypertensitivity to the active substance or any of excipients.

Warnings and Precautions

Mortality. Flecainide was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group. This rate was 16/315 (5.1%) for flecainide and 7/309 (2.3%) for the matched placebo. The average duration of treatment with flecainide in this study was ten months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain, but at present, it is prudent to consider the risks of Class IC agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Ventricular Pro-arrhythmic Effects in Patients with Atrial Fibrillation/ Flutter. A review of the world literature revealed reports of 568 patients treated with oral flecainide 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 (CAF), 10.5% (2) experienced VT or VF. 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 have included increased PVCs, 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 the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive flecainide. Concomitant negative chronotropic therapy such as digoxin or beta-blockers may lower the risk of this complication.

Electrolyte disturbances should be corrected before using Flecainide.

Since flecainide elimination from the plasma can be markedly slower in patients with significant hepatic impairment, flecainide should not be used in such patients unless the potential benefits clearly outweigh the risks. Plasma level monitoring is strongly recommended in these circumstances.

Flecainide is known to increase endocardial pacing thresholds, i.e. to decrease endocardial pacing sensitivity. This effect is reversible and is more marked on the acute pacing threshold than on the chronic. Flecainide should thus be used with caution in all patients with permanent pacemakers or temporary pacing electrodes, and should not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitable pacing rescue is available.

Generally, a doubling of either pulse width or voltage is sufficient to regain capture, but it may be difficult to obtain ventricular thresholds less than 1 Volt at initial implantation in the presence of Flecainide.

The minor negative inotropic effect of flecainide may assume importance in patients predisposed to cardiac failure. Difficulty has been experienced in defibrillating some patients. Most of the cases reported had pre-existing heart disease with cardiac enlargement, a history of myocardial infarction, athero-sclerotic heart disease and cardiac failure. Flecainide should be avoided in patients with structural organic heart disease or abnormal left ventricular function. Flecainide should be used with caution in patients with acute onset of atrial fibrillation following cardiac surgery. In a large scale, placebo-controlled reported clinical trial in post-myocardial infarction patients with asymptomatic ventricular arrhythmia, oral flecainide was associated with a 2.2 fold higher incidence of mortality or non-fatal cardiac arrest as compared with its matching placebo. In that same study, an even higher incidence of mortality was observed in flecainide-treated patients with more than one myocardial infarction. Comparable placebo-controlled clinical trials have not been done to determine if flecainide is associated with higher risk of mortality in other patient groups.

Drug Interaction

Flecainide is a class I anti-arrhythmic and interactions are possible with other anti-arrhythmic drugs where additive effects may occur or where

drugs interfere with the metabolism of flecainide. The following known categories of drugs may interact with flecainide:

Cardiac glycosides: Flecainide can cause the plasma *digoxin* level to rise by about 15%, which is unlikely to be of clinical significance for patients with plasma levels in the therapeutic range. It is recommended that the *digoxin* plasma level in digitalised patients should be measured not less than six hours after any *digoxin* dose, before or after administration of flecainide.

Class II anti-arrhythmics: the possibility of additive negative inotropic effects of beta-blockers, and other cardiac depressants such as verapamil, with flecainide should be recognised

Class III anti-arrhythmics: when flecainide is given in the presence of *amiodarone*, the usual flecainide dosage should be reduced by 50% and the patient monitored closely for adverse effects. Plasma level monitoring is strongly recommended in these circumstances.

Class IV anti-arrhythmics: use of flecainide with other sodium channel blockers is not recommended.

Anti-depressants: *fluoxetine* increases plasma flecainide concentration; increased risk of arrhythmias with *tricyclics*; manufacturer of *reboxetine* advises caution.

Anti-epileptics: limited data in patients receiving known enzyme inducers (*phenytoin, phenobarbital, carbamazepine*) indicate only a 30% increase in the rate of flecainide elimination.

Anti-psychotics: *clozapine* - increased risk of arrhythmias Anti-histamines: increased risk of ventricular arrhythmias with *mizolastine* and *terfenadine* (avoid concomitant use)

Anti-malarials: *quinine* increases plasma concentration of flecainide.

Antivirals: plasma concentration increased by *ritonavir, lopinavar* and *indinavir* (increased risk of ventricular arrhythmias (avoid concomitant use)

Diuretics: Class effect due to hypokalaemia giving rise to cardiac toxicity.

Ulcer healing drugs: *cimetidine* inhibits metabolism of flecainide. In healthy subjects receiving *cimetidine* (1g daily) for one week, plasma flecainide levels increased by about 30% and the half-life increased by about 10%.

Anti-smoking aids: Co-administration of *bupropion* with drugs that are metabolized by CYP2D6 isoenzyme including flecainide, should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If *bupropion* is added to the treatment regimen of a patient already receiving flecainide, the need to decrease the dose of the original medication should be considered.

Treatment with Flecainide is compatible with use of oral anti-coagulants.

Pregnancy and Lactation

There is no evidence as to drug safety in human pregnancy. In New Zealand White rabbits high doses of flecainide caused some foetal abnormalities, but these effects were not reported in Dutch Belted rabbits or rats. The relevance of these findings to humans has not been established. Data have reported that flecainide crosses the placenta to the foetus in patients taking flecainide during pregnancy. Flecainide is excreted in human milk and appears in concentrations which reflect those in maternal blood. The risk of adverse effects to the nursing infant is very small.

ADVERSE EFFECTS

Body as a Whole: Asthenia, fatigue, fever, oedema.

Cardiovascular: Pro-arrhythmic effects occur but are most likely in patients with structural heart disease and/or significant left ventricular impairment.

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 the injection for acute conversion.

This effect is usually short lived and abates quickly following cessation of therapy. The following adverse effects have also been reported- AV block-second-degree and third degree, bradycardia, cardiac failure/congestive cardiac failure, chest pain, hypotension, myocardial infarction, palpitation and sinus pause or arrest and tachycardia (AT or VT).

Skin and Appendages: A range of allergic skin reactions have been reported including rashes, alopecia and rare but serious reports of urticaria. There have also been isolated cases of photosensitivity.

Immune System: A small number of cases of increases in anti-nuclear antibodies have been reported, with and without systemic inflammatory involvement.

Haematological: Reductions in red blood cells white blood cells and platelets have been occasionally reported. These changes are usually mild.

Psychiatric: Rarely, hallucinations, depression, confusion, amnesia. Anxiety and insomnia have been reported.

Gastrointestinal: Occasionally nausea and vomiting. The following have also been reported: abdominal pain, anorexia, constipation, diarrhoea, dyspepsia and flatulence (bloating).

Liver and Bilary System: A number of cases of elevated liver enzymes and jaundice have been reported in association with Flecainide treatment. So far this has always been reversible on stopping treatment. Hepatic dysfunction has also been reported.

Neurological: Most commonly giddiness, dizziness and lightheadedness, which are usually transient. Rare instances of dyskinesia have been reported, which have improved on withdrawal of flecainide therapy. Rare instances of convulsions, and during long term therapy a few cases of peripheral neuropathy; paraesthesia and ataxia have been reported. There also have been reports of flushing, headache, hypoaesthesia, increased sweating, somnolence, syncope, tinnitus, tremor and vertigo.

Ophthalmological: Visual disturbances, such as double vision and blurring of vision may occur but these are usually transient and disappear upon continuing or reducing the dosage. Extremely rare cases of corneal deposits have also been reported.

Respiratory: Dyspnoea and rare cases of pneumonitis have been reported.

OVERDOSE

Overdosage with flecainide is a potentially life threatening medical emergency. No specific antidote is known. There is no known way of rapidly removing flecainide from the system, but forced acid diuresis may theore tically be helpful. Neither dialysis nor haemoperfusion is helpful and injections of anticholinergics are not recommended. Treatment may include therapy with an inotropic agent, intravenous calcium, giving circulatory assistance (e.g. balloon pumping), mechanically assisting respiration, or temporarily inserting a transvenous pacemaker if there are severe conduction disturbances or the patient's left ventricular function is otherwise compromised.

DOSAGE AND ADMINISTRATION

Adults:

Supraventricular arrhythmias: The recommended starting dosage is 50mg twice daily and most patients will be controlled at this dose. If required the dose may be increased to a maximum of 300mg daily.

Ventricular arrhythmias: The recommended starting dosage is 100mg twice daily. The maximum daily dose is 400mg and this is normally reserved for patients of large build or where rapid control of the arrhythmia is required.

After 3-5 days it is recommended that the dosage be progressively adjusted to the lowest level which maintains control of the arrhythmia. It may be possible to reduce dosage during long-term treatment.

Children: Flecainide is not recommended in children under 12, as there is insufficient evidence of its use in this age group.

Elderly Patients: The rate of flecainide elimination from plasma may be reduced in elderly people. This should be taken into consideration when making dose adjustments.

Plasma levels: Based on PVC suppression, it appears that plasma levels of 200-1000 ng/ml may be needed to obtain the maximum therapeutic effect. Plasma levels above 700-1000 ng/ml are associated with increased likelihood of adverse experiences

Dosage in impaired renal function: In patients with significant renal impairment (creatinine clearance of 35ml/min/1.73 sq.m. or less) the maximum initial dosage should be 100mg daily (or 50mg twice daily).

When used in such patients, frequent plasma level monitoring is strongly recommended.

It is recommended that intravenous treatment with Flecainide should be initiated in hospital.

Treatment with oral Flecainide should be under direct hospital or specialist supervision for patients with:

a) AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways.

b) Paroxysmal atrial fibrillation in patients with disabling symptoms.

Treatment for patients with other indications should continue to be initiated in hospital

EXPIRY DATE

Do not use later than date of expiry.

STORAGE:

Store protected from light and moisture, at a temperature not exceeding 30°C. Keep out of reach of children

PRESENTATION:

FLECARITE 50 and FLECARITE 100 are available in blister strips packs of 10 tablets.

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Vill. Bhud & Makhnu Majra, Baddi-173 205,
Teh. Nalagarh, Dist. Solan (H.P.), INDIA.

1298

PRODUCT NAME	: FLECARITE	**COUNTRY :** Domestic	**LOCATION :** Baddi	**SUPERSEDES A/W NO. :**			
ITEM / PACK	: Insert	**NO. OF COLORS:** 1	**REMARK :**				
DESIGN STYLE	: Front -Back	**PANTONE SHADE NOS.:**	**SUBSTRATE :**				
CODE	: 8037279-805	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	: 180 x 240 mm		Prepared By	**Pkg.Dev**			
THERAPEUTIC RANGE	: Cardiovascular		Reviewed By	**Pkg.Dev**			
ART WORK SIZE	: S/S			**CR**			
DATE	: 10-10-2012			**RA**			
			Approved By	**CQA**			

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.