SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flecainide Acetate Tablets 50mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg Flecainide Acetate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
White, circular, biconvex, uncoated tablets embossed “C” on the face and the identifying letters “FI” on the reverse

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Treatment of AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways, when other treatment has been ineffective.

- Treatment of severe symptomatic and life-threatening paroxysmal ventricular arrhythmia which has failed to respond to other forms of therapy or where other treatments have not been tolerated.

- Treatment of paroxysmal atrial arrhythmias (atrial fibrillation, atrial flutter and atrial tachycardia) in patients with disabling symptoms after conversion provided that there is definite need for treatment on the basis of severity of clinical symptoms, when other treatment has been ineffective. Structural heart disease and/or impaired left ventricular function should be excluded because of the increased risk for pro-arrhythmic effects.

4.2 Posology and method of administration

Posology

Adults:
Supraventricular arrhythmias: The recommended starting dose 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 dose 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.

Paediatric population:
Flecainide is not recommended for children under 12 years of age, 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 200-1000ng/ml may be needed to obtain the maximum therapeutic effect. Plasma levels above 700-1000ng/ml are associated with increased likelihood of adverse experiences.

Renal impairment:
In patients with significant renal impairment (creatinine clearance of 35ml/min/1.73sq.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 hospitals.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Flecainide is contraindicated in patients with left ventricular dysfunction or cardiac failure and in patients with a history of myocardial infarction who

have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.

- Flecainide Acetate is contraindicated in the presence of cardiogenic shock.
- It is also contraindicated 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.
- Known Brugada syndrome.
- 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.

4.4 Special warnings and precautions for use

Continuous ECG monitoring is recommended in all patients receiving bolus injection.

Electrolyte disturbances (e.g. hypo- and hyperkalaemia) should be corrected before using flecainide (see section 4.5 for some drugs causing electrolyte disturbances).

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, arterio-sclerotic heart disease and cardiac failure.

Flecainide has been shown to increase mortality risk of post-myocardial infarction patients with asymptomatic ventricular arrhythmia.

Flecainide, like other antiarrhythmics, may cause proarrhythmic effects, i.e. it may cause the appearance of a more severe type of arrhythmia, increase the frequency of an existing arrhythmia or the severity of the symptoms (see section 4.8).

Flecainide should be used with caution in patients with impaired renal function (creatinine clearance ≤ 35 ml/min/1.73 m^2) and therapeutic drug monitoring is recommended.

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

Paediatric population

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

Severe bradycardia or pronounced hypotension should be corrected before using flecainide.

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.

Flecainide prolongs the QT interval and widens the QRS complex by 12-20 %. The effect on the JT interval is insignificant.

A Brugada syndrome may be unmasked due to flecainide therapy. In the case of development of ECG changes during treatment with flecainide that may indicate Brugada syndrome, consideration to discontinue the treatment should be made.

Tambocor was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centre, randomised, double-blind study in patients with asymptomatic non-life-threatening arrhythmias who had 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 Tambocor compared with that seen in a carefully matched placebo-treated group. This rate was 16/316 (5.1%) for Tambocor and 7/309 (2.3%) for its matched placebo. The average duration of treatment with Tambocor in this study was 10 months. It was noted that the increased risk from sudden cardiac death occurred in patients with a history of multiple previous myocardial infarction, usually with poor ventricular function.

Dairy products (milk, infant formula and possibly yoghurt) may reduce the absorption of flecainide in children and infants. Flecainide is not approved for use in children below the age of 12 years; however flecainide toxicity has been reported during treatment with flecainide in children who reduced their intake of milk, and in infants who were switched from milk formula to dextrose feedings.

Flecainide as a narrow therapeutic index drug requires caution and close monitoring when switching a patient to a different formulation.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For further warnings and precautions please refer to section 4.5.

4.5 Interaction with other medicinal products and other forms of 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. Flecainide should not be administered concomitantly with other class I antiarrhythmic.

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 antiarrhythmics: The possibility of additive negative inotropic effects of betablockers and other cardiac depressants such as verapamil with flecainide should be recognised.

Class III antiarrhythmics: 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 antiarrhythmics: The use of flecainide with calcium channel blockers, e.g. *verapamil*, is not recommended.

Life-threatening or even lethal adverse events due to interactions causing increased plasma concentrations may occur (see section 4.9). Flecainide is metabolized by CYP2D6 to a large extent, and concurrent use of drugs inhibiting (e.g. antidepressants, neuroleptics, propranolol, ritonavir, some antihistamines) or inducing (e.g. phenytoin, phenobarbital, carbamazepine) this iso-enzyme can increase or decrease plasma concentrations of flecainide, respectively (see below).

An increase of plasma levels may also result from renal impairment due to a reduced clearance of flecainide (see section 4.4).

Hypokalaemia but also hyperkalaemia or other electrolyte disturbances should be corrected before administration of flecainide. Hypokalaemia may result from the concomitant use of diuretics, corticosteroids or laxatives.

Antidepressants: *Fluoxetine*, *Paroxetine* and other antidepressants increases plasma flecainide concentration; increased risk of arrhythmias with *tricyclics;* manufacturer of reboxetine advises caution.

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

Antipsychotics: *Clozapine* – increased risk of arrhythmias.

Antihistamines: Increased risk of ventricular arrhythmias with *mizolastine* and *terfenadine* (avoid concomitant use).

Antimalarials: Q*uinine* increases plasma concentrations of flecainide.

Antivirals: Plasma concentrations are increased by *ritonavir* (increased risk of ventricular arrhythmias) (avoid concomitant use).

Diuretics: Class effect due to hypokalaemia giving rise to cardiotoxicity.

H2 antihistamines (for the treatment of gastric ulcers): The H2 antagonist *cimetidine* inhibits metabolism of flecainide. In healthy subjects receiving *cimetidine* (1 g daily) for 1 week, plasma flecainide levels increased by about 30 % and the half-life increased by about 10 %.

Antismoking 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence as to drug safety in human pregnancy. Data have shown that flecainide crosses the placenta to the foetus in patients taking flecainide during pregnancy. Flecainide should only be used in pregnancy if the benefit outweighs the risks.

Breast-feeding

Flecainide is excreted in human milk. Plasma concentrations obtained in a nursing infant are 5-10 times lower than therapeutic drug concentrations (see section 5.2). Although the risk of adverse effects to the nursing infant is very small, flecainide should only be used during lactation if the benefit outweighs the risks.

4.7 Effects on ability to drive and use machines

Flecainide Tablets have no or negligible influence on the ability to drive and use machines. However, driving ability, operation of machinery and work without a secure fit may be affected by adverse reactions such as dizziness and visual disturbances, if present.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/l0), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000) and very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

- Blood and lymphatic system disorders:
  Uncommon: red blood cell count decreased, white blood cell count decreased and platelet count decreased.

- Immune system disorders:
  Very rare: antinuclear antibody increased with and without systemic inflammation.

- Psychiatric disorders:
  Rare: hallucination, depression, confusional state, anxiety, amnesia, insomnia.

- Nervous system disorders:
  Very common: dizziness, which is usually transient. .
  Rare: paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache,peripheral neuropathy, convulsions, dyskinesia.

- Eye disorders:
  Very common: visual impairment, such as diplopia and vision blurred.
  Very rare: corneal deposits.

- Ear and labyrinth disorders:
  Rare: tinnitus, vertigo

- Cardiac disorders:
  Common: pro-arrhythmia (most likely in patients with structural heart disease and/or significant left ventricular impairment).
  Not known: Dose-related increases in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4).
  Uncommon: Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate
  Not known: atrioventricular block second degree and atrioventricular block third degree, cardiac arrest, bradycardia, cardiac failure/ cardiac failure congestive, chest pain, hypotension, myocardial infarction, palpitations, sinus pause or arrest, and tachycardia (AT or VT) or ventricular fibrillation. Demasking of a pre-existing Brugada syndrome.

- Respiratory, thoracic and mediastinal disorders:
  Common: dyspnoea
  Rare: pneumonitis
  Not known: pulmonary fibrosis, interstitial lung disease

- Gastrointestinal disorders:
  Uncommon: nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence

- Hepatobiliary disorders:
  Rare: hepatic enzymes increased with and without jaundice.
  Not known: hepatic dysfunction

- Skin and subcutaneous tissue disorders:
  Uncommon: dermatitis allergic, including rash, alopecia
  Rare: serious urticaria
  Very rare: photosensitivity reaction

- Musculoskeletal and connective tissue disorders:
  Not known: arthralgia and myalgia

- General disorders and administration site conditions:
  Common: asthenia, fatigue, pyrexia, oedema

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosage with flecainide is a potentially life-threatening medical emergency. Increased drug susceptibility and plasma levels exceeding therapeutic levels may also result from drug interaction (see section 4.5). No specific antidote is known. There is no known way to rapidly remove flecainide from the system, but forced acid diuresis may theoretically be helpful. Neither dialysis nor haemoperfusion is effective and injections of anticholinergics are not recommended.

Treatment should be supportive and may include removal of unabsorbed drug from the GI tract. Intravenous 8.4 % sodium bicarbonate reduces flecainide activity. Further measures may include inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol as well as mechanical ventilation and circulatory assistance (e.g. balloon pumping). Temporarily inserting a transvenous pacemaker in the event of conduction block should be considered. Assuming a plasma half-life of approximately 20 h, these supportive treatments may need to be continued for an extended period of time. Forced diuresis with acidification of the urine theoretically promotes drug excretion. Intravenous fat emulsion and ECMO could be considered on a case-by-case basis.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, antiarrhythmics, class Ic.
ATC code: C01BC04

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.

5.2 Pharmacokinetic properties

Oral administration of flecainide results in extensive absorption, with bioavailability approaching 90 to 95%. Flecainide does not appear to undergo significant hepatic first-pass metabolism. In patients, 200 to 600 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%.

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. The volume of distribution is 8.7 L/kg.

5.3 Preclinical safety data

In New Zealand white rabbits, high doses of flecainide produced some embryotoxic effects (increased resorption) and teratogenic effects (increased incidence of clubbed paws and skeletal abnormalities in sternebrae and vertebrae). Based on mg/kg body weight a safety margin of 8.7 for embryotoxic effects and 10.5 for teratogenic effects was calculated. These effects were not seen in Dutch belted rabbits or rats. The relevance of these findings to humans has not been established. Prolongation of gestation was seen in rats under a dose of 50 mg/kg. No effects on fertility were observed. No human data concerning pregnancy and lactation are available.

6.1 List of excipients

Croscarmellose sodium,
magnesium stearate,
maize starch,
pregelatinised maize starch
microcrystalline cellulose (E460).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Polypropylene containers
Do not store above 25°C.
Store in the original container.

Blister packs
Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

The blister packs are manufactured from 250µm white rigid PVC coated with 60gm^{-2} PVDC and 20µm hard temper aluminium foil. The polypropylene containers are manufactured from rigid injection moulded polypropylene with snap-on polyethylene lids.

Pack sizes:
Blister: 20s, 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s.
Tablet container: 100s, 250s, 500s, 1000s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0430

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

18/06/2024