# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Flecainide acetate 25 mg/5 ml oral solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Flecainide acetate 25 mg/5 ml oral solution contains 25 mg flecainide acetate, equivalent to 21.8 mg of flecainide.

Excipients with known effect

Each 5 ml of Flecainide acetate 25 mg/5 ml oral solution contains 4.0 mg sodium benzoate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Oral Solution

Clear, colourless solution with characteristic cherry odour.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Flecainide oral solution is indicated for:
AV nodal reciprocating tachycardia, arrhythmias associated with Wolff-Parkinson- White Syndrome and similar conditions with accessory pathways.
Paroxysmal atrial fibrillation in patients with disabling symptoms when treatment need has been established and in the absence of left ventricular dysfunction (see section 4.4 Special warnings and special precautions for use).
Arrhythmias of recent onset will respond more readily.
Symptomatic sustained ventricular tachycardia.
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 oral solution can be used for the maintenance of normal rhythm following conversion by other means.

## 4.2 Posology and method of administration

Posology

*Adults*

Supraventricular arrhythmias: The recommended starting dosage is 50 mg (10 ml of the oral solution) twice daily and most patients will be controlled at this dose. If required, the dose may be increased to a maximum of 300 mg daily (60 ml of the oral solution).

Ventricular arrhythmias: The recommended starting dosage is 100 mg (20 ml of the oral solution) twice daily.

The maximum daily dose is 400 mg (80 ml of the oral solution) 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 oral solution is not recommended in children under 12, as there is insufficient evidence of its use in this age group.

*Elderly*

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.

Renal impairment: In patients with significant renal impairment (creatinine clearance of 35 ml/min/l.73 sq.m. or less) the maximum initial dosage should be 100 mg (20 ml of the oral solution) daily (or 50 mg (10 ml of the oral solution) 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 Flecainide oral solution should be under direct hospital or specialist supervision for patients with:

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

Paroxysmal atrial fibrillation in patients with disabling symptoms.

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

Method of administration

Flecainide oral solution is for oral use. In order to avoid the possibility of food affecting the absorption of the drug, flecainide should be taken on an empty stomach or one hour before food.

A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a "Press-In" Bottle Adapter (PIBA) are provided with the product.

Open the bottle and at first use insert the "Press-In" Bottle Adapter (PIBA).

Insert the syringe into the PIBA and draw out the required volume from the inverted bottle.

Remove the filled syringe from the bottle in the upright position.

Discharge the syringe contents into the mouth. Repeat steps 2 to 4 as needed to achieve the required dose.

Replace the cap on the bottle (PIBA remains in place).

The oral syringe must be rinsed thoroughly with water after each use by taking the two parts of syringe apart. Allow the parts to air dry afterwards.

## 4.3 Contraindications

Hypersensitivity to flecainide acetate or to any of the excipients listed in section 6.1.

Flecainide is contraindicated in cardiac failure and in patients with a history of myocardial infarction who have either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia.

Flecainide 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 atrioventricular block, bundle branch block or distal block.

## 4.4 Special warnings and precautions for use

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 anti-arrhythmics, 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.

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.

In a large scale, placebo-controlled 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.

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.

Liquid flecainide formulations may have a local anaesthetic effect on the mouth. Patients may be advised to avoid eating until any anaesthetic effect has worn off.

For further warnings and precautions please refer to section 4.5 (Interaction).

**Flecainide acetate 25 mg/5 ml oral solution contains sodium benzoate and sodium.**

This medicinal product contains 4.0 mg sodium benzoate in each 5 ml.

This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml, that is to say essentially 'sodium-free'.

## 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 anti-arrhythmics.

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.

Life-threatening or even lethal adverse events due to interactions causing increased plasma concentrations may occur (see section 4.9). Flecainide is metabolised 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.

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.

Anti-depressants: fluoxetine, paroxetine and other antidepressants increase 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.

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

Antimalarials: quinine increases plasma concentration of flecainide.

Antivirals: plasma concentration increased by ritonavir, lopinavir and indinavir (increased risk of ventricular arrhythmias); avoid concomitant use.

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

H2 antihistamines (for the treatment of gastric ulcers): cimetidine inhibits metabolism of flecainide. In healthy subjects receiving cimetidine (l g 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.

Anticoagulants: Treatment with flecainide is compatible with use of oral anticoagulants.

## 4.6 Fertility, Pregnancy and lactation

Pregnancy

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 seen in Dutch Belted rabbits or rats (see section 5.3). The relevance of these findings to humans has not been established. 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.

Fertility

In animal experiments, research showed that flecainide had no effect on fertility. There are no human data on the effect of flecainide on female fertility.

## 4.7 Effects on ability to drive and use machines

Flecainide acetate 25 mg/5 ml oral solution has no or negligible influence on the ability to drive and use machines. However, driving ability, operation of machinery and working without a secure fit may be affected by adverse reactions such as dizziness and visual disturbances (if present).

## 4.8 Undesirable effects

Adverse effects have been ranked under headings of frequency using the following convention: 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); frequency not known (cannot be estimated from the available data).

| **System Organ Class** | **Very Common (≥1/10)** | **Common (≥1/100 to <1/10)** | **Uncommon (≥1/1,000 to <1/100)** | **Rare (≥1/10,000 to <1/1,000)** | **Very rare (< 1/10,000)** | **Not known: (cannot be established from the available data)** |
|---|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | Red blood cell count decreased, white blood cell count decreased, and platelet count decreased. | | | |

| System Organ Class | Very Common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Very rare (< 1/10,000) | Not known: (cannot be established from the available data) |
|---|---|---|---|---|---|---|
| Immune system disorders | | | | | Antinuclear antibody increased with and without systemic inflammation. | |
| Psychiatric disorders | | | | Hallucination, depression, confusional state, anxiety, amnesia, insomnia. | | |
| Nervous system disorders | Dizziness, which is usually transient. | | | Paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, convulsion, dyskinesia. | | Local anaesthesia to the mouth* |
| Eye disorders | Visual impairment, such as diplopia and vision blurred. | | | | Corneal deposits | |
| Ear and labyrinth disorders | | | | Tinnitus, vertigo. | | |

| System Organ Class | Very Common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Very rare (< 1/10,000) | Not known: (cannot be established from the available data) |
|---|---|---|---|---|---|---|
| Cardiac disorders | | Proarrhythmia (most likely in patients with structural heart disease and/or significant left ventricular impairment). | Patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate. | | | Dose-related increases in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4). 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 | | Dyspnoea | | Pneumonitis | | Pulmonary fibrosis, interstitial lung disease. |

| System Organ Class | Very Common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Very rare (< 1/10,000) | Not known: (cannot be established from the available data) |
|---|---|---|---|---|---|---|
| Gastrointestinal disorders | | | Nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence. | | | |
| Hepatobiliary disorders | | | | Hepatic enzymes increased with and without jaundice. | | Hepatic dysfunction |
| Skin and subcutaneous tissue disorders | | | Dermatitis allergic, including rash, alopecia. | Serious urticaria | Photosensitivity reaction | |
| Musculoskeletal and connective tissue disorders | | | | | | Arthralgia and Myalgia |
| General disorders and administration site conditions | | Asthenia, fatigue, pyrexia, oedema. | | | | |

*This adverse effect relates specifically to the liquid formulation.

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 at 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. Neither dialysis nor haemoperfusion is effective.

Treatment should be supportive and may include removal of unabsorbed drug from the GI tract. 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.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Class 1 anti-arrhythmic (local anaesthetic) agent.

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 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%.

Recovery of unchanged flecainide in urine of healthy subjects was approximately 42% of a 200 mg 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.

### 5.3 Preclinical safety data

One rabbit tribe showed teratogenicity and embryotoxicity under flecainide. This effect was neither present in other rabbit tribes nor in rats or mice.

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 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium benzoate (E211)
Sucralose (E955)
Cherry flavour
Citric acid (E330)
Purified water

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

After first opening use within 1 month.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original bottle in order to protect from light.

### 6.5 Nature and contents of container

Amber, type III glass bottle safely closed with a child resistant, screw cap with tamper evident closure. Each bottle contains 300 ml of this medicinal product. A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a “press in” syringe/bottle adapter are also provided.

### 6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Colonis Pharma Limited
25 Bedford Square,
Bloomsbury,
London,
WC1B 3HH,
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## 8 MARKETING AUTHORISATION NUMBER(S)

PL 41344/0077

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/10/2023

## 10 DATE OF REVISION OF THE TEXT

21/11/2023