SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Felkarid 50 mg tablets
Felkarid 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg or 100 mg flecainide acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Felkarid 50 mg tablets
White to off-white, round, biconvex tablets with diameter 7 mm.

Felkarid 100 mg tablets
White to off-white, round, biconvex tablets with diameter 9 mm and score line on one side.
The tablet can be divided into equal doses.

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.
- Symptomatic sustained ventricular tachyarrhythmia.
- 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.
- Paroxysmal atrial arrhythmias (atrial fibrillation, flutter and tachycardia) in patients with disabling symptoms when treatment need has been established.

Structural heart disease and/or impaired left ventricular function should be excluded because of the increased risk for pro-arrhythmic effects.
Flecainide Acetate tablets can be used for the maintenance of normal rhythm following conversion by other means.

4.2 Posology and method of administration

Posology
Initiation of flecainide acetate therapy and dose adjustments should be made under medical supervision and monitoring of ECG and plasma level.

Hospitalization could be necessary during such procedures for certain patients, especially for patients with life-threatening ventricular arrhythmias. These decisions should be made under supervision of specialist.
In patients with an underlying organic cardiomyopathy and especially those with history of myocardial infarction, flecainide treatment should only be initiated when other antiarrhythmics, which do not belong to class I C (especially amiodarone), are ineffective or not tolerated and when non-pharmacological therapy (surgery, ablation or implanted defibrillator) is not indicated. Close medical supervision of ECG and plasma levels during treatment is required.

Adults:
Supraventricular arrhythmias: the recommended starting dose is 50 mg twice daily. If necessary, the dose may be increased to a maximum of 300 mg per day.

Ventricular arrhythmias: the recommended starting dose is 100 mg twice daily. The maximum dose is 400 mg per day 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.

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.

Pediatric patients:
There are insufficient data on the use of flecainide in children. Safety and effectiveness have not been established and therefore flecainide should not be used in children younger than 12 years.

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 35ml/min/1.73m^2 or less) 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.

Reduced liver function:
Patients with impaired liver function should be closely monitored, the dosage should not exceed 100 mg per day.

Patients with a permanent pacemaker in situ should be treated with caution. The dose should not exceed 200 mg per day.

In patients who are treated concomitantly with cimetidine or amiodarone close monitoring is required. In some patients, the dose may need to be reduced and it should not exceed 200 mg per day. These patients should be supervised during initial and maintenance therapy.

Plasma level monitoring and ECG control are recommended at regular intervals (ECG control once a month and long term ECG every 3 months) during therapy. During initiation therapy and when the dose is increased, an ECG should be performed every 2-4 days.

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.

Method of administration

For oral use. The tablets should be taken (with some liquid).

4.3 Contraindications

- Hypersensitivity to the active substance 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.
- Patients with long standing atrial fibrillation in whom there has been no attempt to convert sinus rhythm.
- Patients with impaired ventricular function, cardiogenic shock, severe bradycardia (less than 50 beats per minute) and severe hypotension.
- Use in combination with class I antiarrhythmics (sodium channel blockers).
- In patients with 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 atrioventricular block, bundle branch block or distal block.
- Patients with asymptomatic or mildly symptomatic ventricular arrhythmias should not use flecainide.
- Known Brugada syndrome.

4.4 Special warnings and precautions for use

Treatment with oral flecainide 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.

Starting treatment with flecainide and adjusting the dose should be done under medical supervision and monitoring the ECG and plasma levels. In certain patients, hospitalization may be required during these procedures mainly in patients with potentially life-threatening ventricular arrhythmias.
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 4.8).).
Flecainide should be avoided in patients with structural heart disease or abnormal left ventricular function (see section 4.8).
Disturbances in the electrolyte balance (eg hypo- and hyperkalaemia) should be corrected before flecainide is used (see section 4.5 for medicinal products causing electrolyte disturbances).
Hypokalaemia or hyperkalaemia can affect the action of class I antiarrhythmics. Hypokalaemia may occur in patients who use diuretics, corticosteroids and laxatives.
Severe bradycardia or pronounced hypotension 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 should be used with caution in patients with impared renal function (creatinine clearance ≤ 35ml/min/1.73 m^2) and therapeutic drug monitoring is recommended.
The rate of flecainide elimination from plasma may be reduced in older people. 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 data on the use of flecainide in children.

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

Flecainide has been shown to increase mortality risk of post-myocardial infarction patients with asymptomatic ventricular arrhythmia.
An acceleration of the ventricular degree of atrial fibrillation in the case of treatment failure occurred.
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 the development of ECG changes during treatment with flecainide that may indicate Brugada syndrome, consideration to discontinue the treatment should be made.

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. Dairy products (milk, infant formula and possible yoghurt) may reduce the absorption of flecainide in children and infants.
For further warnings and precautions, see section 4.5

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

4.5 Interaction with other medicinal products and other forms of interaction

Class I anti-arrhythmics: Flecainide should not be used simultaneously with other class I antiarrhythmic drugs (such as quinidine).

Class II anti-arrhythmics: The possibility of additive negative inotropic effects of class II anti-arrhythmics such as beta-blockers, if taken simultaneously with flecainide should be considered.

Class III anti-arrhythmics: If 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: The use of flecainide with other calcium channel blockers, eg. *verapamil* should be considered with caution.
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 with risk of cardiotoxicity.

Anti-histamines: Increased risk of ventricular arrhythmias with *mizolastine, astemizole* and *terfenadine* (avoid concomitant use).

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

Anti-depressants: Paroxetine, *fluoxetine*, and other antidepressants increases plasma flecainide concentration; increased risk of arrhythmias with *tricyclic* anti-depressants.

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*, *haloperidol* and *risperidol* - increased risk of arrhythmias.

Anti-malarials: *Quinine* and *halofantrine* increase plasma concentration of flecainide.

Antifungals: *Terbinafine* may increase plasma concentrations of flecainide resulting from its inhibition of CYP2D6 activity.

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

Anti-smoking aids: Co-administration of *bupropion* (metabolised by CYP2D6) with 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.

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 digitalized patients should be measured not less than six hours after any *digoxin* dose, before or after administration of flecainide.

Anticoagulants: The treatment with flecainide is compatible with the 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 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. If flecainide is used during pregnancy maternal flecainide plasma levels should be monitored throughout pregnancy.

Breastfeeding
Flecainide is excreted in human milk. Plasma concentrations obtained in a nursing infant are 5-10 times lower than therapeutic drug concentrations (see 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 acetate has a negligible moderate influence on driving ability and on ability to operate machinery. The driving ability, operation of machines and working without a secure fit can be affected by side effects such as dizziness and visual disturbances, if present.

4.8 Undesirable effects

Like other anti-arrhythmics, flecainide can induce an arrhythmia.
The existing arrhythmia can worsen or a new arrhythmia may develop. The risk of proarrhythmic effects is most likely in patients with structural heart disease and / or significant left ventricular impairment.
The most common cardiovascular side effects are second and third degree AV block, bradycardia, heart failure, chest pain, myocardial infarction, hypotension, sinus arrest, tachycardia (AT and VT) and palpitations.
The most common side effects are dizziness and visual disturbances that occur in approximately 15% of the treated patients. These side effects are usually transient and disappear after discontinuation of treatment or a reduction in dose.
The following list of side effects is based on experiences from clinical studies and experiences after the medicinal product has been marketed.

The side effects are listed below according to system organ classes and frequency. The frequencies are defined as:
Very common (≥1 / 10)
Common (≥1 / 100 and <1/10)
Uncommon (≥1 / 1000 and <1/100)
Rare (≥1 / 10,000 and <1/1000)
Very rare (<1 / 10,000)
Not known (can not be determined 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, confusion, anxiety, amnesia, insomnia.

Nervous system disorders:
Very common: dizziness, giddiness and light-headedness usually transient.
Rare: paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, 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: Proarrhythmia (most likely in patients with structural heart disease).
Uncommon: patients with atrial fibrillation can develop 1: 1 AV conduction with increased heart rhythm. Frequency not known (cannot be estimated from the available data). Dose related increases in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4). Second and third degree AV block, cardiac arrest, bradycardia, heart failure / congestive heart failure, chest pain, hypotension, myocardial infarction, palpitations, sinus 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.
Frequency not known: pulmonary fibrosis, interstitial lung disease.

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

Hepatobiliary disorders:
Rare: increased level of hepatic enzyme with or without jaundice.
Frequency not known: hepatic dysfunction.

Skin and subcutaneous tissue disorders:
Uncommon: allergic dermatitis, including rash, alopecia.
Rare: serious urticarial.
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, feeling of discomfort.

4.9 Overdose

Overdose with flecainide is a potentially life-threatening medical emergency. Drug interactions can also lead to increased sensitivity to drug or to plasma levels higher than therapeutic (see section 4.5). Overdose can lead to hypotension, seizures, bradycardia, conduction delays (sinoarterial or AV block) and asystole. The QRS and QT intervals are extended and ventricular arrhythmias may occur. Flecainide can slow or reverse atrial fibrillation in atrium flutter with fast conduction.
There is no known way to rapidly remove flecainide from the system. Dialysis and hemoperfusion are not effective. If possible, removal of unabsorbed drug from the gastrointestinal tract. Forced diuresis with acidification of the urine promotes in theory the excretion of the drug. Intravenous lipid emulsion could reduce the effective free concentration of flecainide.

No specific antidote is known. Intravenous sodium bicarbonate 8.4% often reduces flecainide activity at a receptor level within a few minutes.
Further measures must be supportive and may consist of administration of inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol, as well as mechanical ventilation and circulatory assisstance (eg. a balloon pump).
Temporarily inserting a transvenous pacemaker, in the event of conduction block should be considered. In individual cases, Extra Corporal Membrane Oxygenation (ECMO) should be considered. Assuming a plasma half-life of approximately 20 hours, it may be necessary for these support measures to be carried out for an extended period of time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-arrhythmics Class Ic, Flecainide, ATC code: C01BC04

Flecainide belongs to the class Ic antiarrhythmics, which are used for the treatment of severe symptomatic ventricular and supraventricular arrhythmias. It should not be used in the suppression of asymptomatic ventricular arrhythmias in patients with a history of myocardial infarction. Most side effects are on the central nervous system.

Electrophysiologically, flecainide is a local anesthetic type (class Ic) of antiarrhythmic compound. It is an amide-type local anesthetic, being structurally related to procainamide and encainide as these are also benzamide derivatives.
The characterization of flecainide as a class Ic compound is based on three characteristics: significant depression of the fast sodium channels in the heart; slow onset and offset kinetics of inhibition of the sodium channels (reflecting slow attachment to and dissociation from sodium channels); and the differential effect of the drug on the action potential duration in the ventricular muscle compared to the Purkinje fibers, having no effect in the former and significantly shortening it in the latter.
This composite of properties leads to a significant depression in conduction velocity in fibers dependant on the fast channel fibers for depolarization, but shows a modest increase in the effective refractory period when tested in isolated cardiac tissue. These electrophysiological properties of flecainide may lead

to prolongation of the PR interval and widening of the QRS complex in the ECG. At very high concentrations flecainide exerts a weak depressant effect on the slow channels in the myocardium. This is accompanied by a negative inotropic effect. Flecainide does not have a significant interaction with the autonomic nervous system. The drug does not seem to have a measurable effect on the coronary, pulmonary or other regional circulation systems.

5.2 Pharmacokinetic properties

Absorption
Flecainide acetate is almost completely absorbed after oral administration and does not undergo extensive first-pass metabolism. The bioavailability of flecainide acetate tablets is about 90%. The therapeutic plasma concentration range is generally from 200 to 1000 ng / ml.

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

Biotransformation
Flecainide is extensively metabolised (undergoes genetic polymorphism), of which the two main metabolites are m-O-dealkylated flecainide and m-O-dealkylated lactam of flecainide, both may exhibit some activity.

Elimination
It is largely excreted in the urine, about 30% as unchanged flecainide and the rest as metabolites. Approximately 5% is excreted in the faeces. The elimination half-life time of flecainide is about 20 hours. With hemodialysis, approximately 1% of the unchanged flecainide is removed.
Excretion of flecainide is decreased in renal failure, heart failure and in alkaline urine.

5.3 Preclinical safety data

The only preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC are the following effects found on the reproduction. In one breed of rabbits, flecainide was found to be teratogenic and embryotoxic. There were insufficient data to establish a safety margin for this effect. However, these effects were not seen in another breed of rabbits, rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, pregelatinized (Partially pregelatinized maize starch)
Croscarmellose sodium
Microcrystalline cellulose
Hydrogenated Vegetable Oil (Botanical source: Gossypium)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Felkarid tablets are packed in PVC/PVDC/Aluminium foil blisters.
Box containing 30 tablets in blisters is available.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT