SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Flecaïnideacetaat ratiopharm 100 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg flecainide acetate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White, circular, biconvex, uncoated tablets (diameter approx. 8.5 mm) embossed with a breakline on one face with the identifying letters “C” above the line and “FJ” below, the reverse with a breakline.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of
1. AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways, when other treatment has been ineffective.
2. Severe symptomatic and life-threatening paroxysmal ventricular arrhythmia which has failed to respond to other forms of therapy. Also where other treatments have not been tolerated.
3. 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

<u>Posology</u>
Initiation of flecainide acetate therapy and dose changes 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. The decisions should be made under supervision of a specialist. In patients with an underlying organic cardiopathy and especially those with a history of myocardial infarction, flecainide treatment should only be started when other arrhythmic agents, other than class IC (especially amiodarone), are ineffective or not tolerated and when non-pharmacological treatment (surgery, ablation, implanted defibrillator) is not indicated. Strict medical monitoring of ECG and plasma levels during treatment is required.

Adults and adolescents (13-17 years of age):
Supraventricular arrhythmias: The recommended starting dose is 50 mg 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.

Ventricular arrhythmias: The recommended starting dose is 100 mg twice daily. The maximum daily dose is 400 mg 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:
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).

Children: Flecainide acetate is not recommended for use in children below 12 years of age due to a lack of data on safety and efficacy.

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.

Impaired renal function:
In patients with significant renal impairment (creatinine clearance of ≤ 35 ml/min/1.73sq.m. 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).

Impaired liver function:
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.

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. 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.

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 to sinus rhythm
- Patients with reduced or impaired ventricular function, cardiogenic shock, severe bradycardia (less than 50 bpm), 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 atrio-ventricular block, bundle branch block or distal block.
- Patients with asymptomatic or mildly symptomatic ventricular arrhythmias must not be given 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.

Initiation of flecainide acetate therapy and dose changes should be made under medical supervision and monitoring of ECG and plasma level. Hospitalization could be necessary during such procedures for certain patients, in particular patients with potential 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 section 4.8).

Flecainide should be avoided in patients with structural heart disease or abnormal left ventricular function (see section 4.8).

Electrolyte disturbances (e.g. hypo- and hyperkalaemia) should be corrected before using flecainide (see section 4.5 for some drugs causing electrolyte disturbances). Hypokalaemia or hyperkalaemia may influence the effects of class 1 antiarrhythmic agents. Hypokalaemia may occur in patients who use diuretics, corticosteroids or 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 outweigh the risks. Plasma level monitoring is recommended.

Flecainide should be used with caution in patients with impaired renal function (creatinine clearance ≤ 35ml/min/1.73sq m) 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.

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 rate of atrial fibrillation in case of therapy failure has been reported.
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.

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 possibly yoghurt) may reduce the absorption of flecainide in infants and children.

For further warnings and precautions please refer to section 4.5.

Excipient(s)
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 antiarrhythmics: Flecainide should not be administered concomitantly with other class I antiarrhythmics (e.g. *quinidine*).

Class II antiarrhythmics: The possibility of additive negative inotropic effects of Class II antiarrhythmics, i.e. beta-blockers, with flecainide should be recognised.

Class III antiarrhythmics: 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 antiarrhythmics: The use of flecainide with calcium channel blockers, e.g. *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 metabolised by cytochrome P450 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 in 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* and may increase the risk of cardiotoxicity.

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

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

Antidepressants: *Paroxetine*, *fluoxetine* and other antidepressants increase plasma flecainide concentration; increased risk of arrhythmias with *tricyclics*.

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, haloperidol and risperidone* - increased risk of arrhythmias.

Antimalarials: *Quinine* and *halofantrine* increase plasma concentrations of flecainide.

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

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

H_2 antihistamines (for the treatment of gastric ulcers): The H_2 antagonist *cimetidine* inhibits metabolism of flecainide. In healthy subjects receiving cimetidine (1 g daily) for 1 week, the AUC of flecainide increased by about 30% and the half-life increased by about 10%.

Antismoking 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 digitalised patients should be measured not less than 6 hours after any *digoxin* dose, before or after administration of flecainide.

*Anticoagulant*s: 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 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. 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 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 acetate has moderate influence on the ability to drive and use machines. 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

Like other anti-arrhythmics, flecainide can have the effect of inducing arrhythmia.

The existing arrhythmia may worsen or a new arrhythmia may occur. The risk of pro-arrhythmic effects is most likely in patients with a structural heart disease and/or significant left ventricular impairment.
The most commonly occurring cardiovascular adverse effects are second and third degree AV block, bradycardia, cardiac failure, chest pain, myocardial infarction, hypotension, sinus arrest, tachycardia (AT and VT) and palpitations.

The most common adverse effects are giddiness and visual disturbances that occur in about 15 % of the patients receiving treatment. These adverse effects are usually transient and disappear upon continuing or reducing the dosage. The following list of adverse effects are based on experiences from clinical trials and reported after marketing.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as:
Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000 and <1/1,000)
Very rare (<1/10,000)
Not known (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: giddiness, dizziness and lightheadedness which are usually transient
Rare: paraesthesia, ataxia, hypoaesthesia, hyperhidrosis, syncope, tremor, flushing, somnolence, headache, neuropathy peripheral, convulsion, 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 and/or significant left ventricular impairment)
Uncommon: patients with atrial flutter can develop a 1:1 AV conduction with increased heart rate.
Not known: dose-related increases in PR and QRS intervals may occur (see section 4.4). Altered pacing threshold (see section 4.4). AV-block second-degree and third-degree, cardiac arrest, bradycardia, cardiac failure / cardiac failure congestive, 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
Not known: pulmonary fibrosis, interstitial lung disease

Gastrointestinal disorders
Uncommon: nausea, vomiting, constipation, abdominal pain, decreased appetite, diarrhoea, dyspepsia, flatulence, dry mouth, taste disturbances

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
Uncommon: arthralgia, myalgia (possibly with fever)

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

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 national reporting system listed in Appendix V.

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).
Overdose can lead to hypotension, seizures, bradycardia, conduction delay (sinoatrial or AV block) and asystole. The QRS and QT intervals are extended and ventricular arrhythmias may occur. Flecainide can slow or reverse atrial fibrillation into atrium flutter with fast conduction.

There is no known way to rapidly remove flecainide from the system. Neither dialysis nor haemoperfusion is effective. If possible, unabsorbed drug should be removed from the GI tract. Forced diuresis with acidification of the urine theoretically promotes drug excretion. Intravenous fat emulsion could decrease the effective free concentration of flecainide.

No specific antidote is known.
Intravenous sodium bicarbonate 8.4 % often reduces flecainide activity at the receptor level within minutes.

Further measures should be supportive and may include inotropic agents or cardiac stimulants such as dopamine, dobutamine or isoproterenol as well as mechanical ventilation and circulatory assistance (e.g. ballon pumping).
Temporarily inserting a transvenous pacemaker in the event of conduction block should be considered. In individual cases, Extra Corporal Membrane Oxygenation (ECMO) may 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics, class IC, Flecainide
ATC code: C01 BC 04

Flecainide acetate is a Class IC antiarrhythmic agent used for the treatment of severe symptomatic life-threatening ventricular arrhythmias and supraventricular arrhythmias.

Electrophysiologically, flecainide is a local anaesthetic-type (Class IC) of antiarrhythmic compound. It is an amide type of local anaesthetic, being structurally related to procainamide and encainide in so far as these agents are also benzamide derivatives.
The characterisation of flecainide as a Class IC compound is based on a triad of features: marked depression of the fast sodium channel in the heart; slow onset and offset kinetics of inhibition of the sodium channel (reflecting slow attachment to and dissociation from sodium channels); and the differential effect of the drug on the action potential duration in ventricular muscle versus Purkinje fibres, having no effect in the former and markedly shortening it in the latter. This composite of properties leads to a marked depression in conduction velocity in fibres dependant on the fast-channel fibres for depolarisation but with a modest increase in the effective refractory period when tested in isolated cardiac tissues. These electrophysiological properties of flecainide acetate may lead to prolongation of the PR-interval and QRS duration on the ECG. At very high concentrations flecainide exerts a weak depressant effect on the slow channel in the myocardium. This is accompanied by a negative inotropic effect.

5.2 Pharmacokinetic properties

Absorption
Flecainide is almost completely absorbed after oral administration and does not undergo extensive first-pass metabolism. The bioavailability from flecainide acetate tablets has been reported to be about 90%.
The therapeutic plasma concentration range is generally accepted as 200 to 1000ng per ml. Given intravenously the mean time to achieve peak serum concentration was 0.67 hours and the mean bioavailability was 98%, compared with 1 hour and 78% for an oral solution and 4 hours and 81% for a tablet.

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
Flecainide is excreted mainly in the urine, approximately 30% as unchanged drug and the remainder as metabolites. About 5% is excreted in the faeces. Excretion of flecainide is decreased in renal failure, liver diseases, heart failure, and in alkaline urine. Haemodialysis removes only about 1% of unchanged flecainide.
The elimination half-life of flecainide is about 20 hours.

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 SPC are the following effects found on reproduction. In one breed of rabbits flecainide caused teratogenicity and embryotoxicity. 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

Croscarmellose sodium (E 468)
Magnesium stearate (E 470b)
Pregelitinized maize starch
Maize starch
Microcrystalline cellulose (E460).

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

PVC/PVDC/Al-blisters and bottles of polypropylene with snap-on polyethylene lids.

Pack sizes:
Blister: 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168 and 180 tablets.
Bottles: 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Ratiopharm GmbH
Graf-Arco-Str.3
89079 Ulm
Duitsland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 34516

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 7 december 2006
Datum van laatste verlenging: 3 mei 2012

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4, 4.5, 4.8 en 4.9: 23 mei 2024

<Detailed information on this medicinal product is available on the website of {name of MS/Agency}>