MIGARID Tablets (Flunarizine hydrochloride)

Composition

MIGARID Tablets 5 mg
Each film-coated tablet contains:
Flunarizine hydrochloride..............................5 mg

MIGARID Tablets 10 mg
Each film-coated tablet contains:
Flunarizine hydrochloride.............................10 mg

Dosage Form

Film-coated tablet

Pharmacology

Pharmacodynamics

Flunarizine (0.01–10 µmol.l⁻¹) inhibits the entry of Ca²⁺ into cells via voltage-gated calcium channels. It has a higher affinity for the T-type compared with the L- and N-type voltage-operated channel. In consequence, it exhibits greater potency against neuronal than non-neuronal calcium channels, inhibiting (to a greater extent than verapamil or diltiazem) the uptake of calcium by cortical synaptosomes, but with less effect on the calcium channels of smooth muscle than the dihydropyridines. Flunarizine inhibits the Ca²⁺-Mg²⁺ ATPase activity of synaptic plasma membranes, decreasing the Vₘₐₓ by 37% with no significant effects on the Kᵣ for Ca²⁺ (162.7 ± 14.9 nM free); this is an effect mediated by the inhibition of the calmodulin interaction with the enzyme.

Flunarizine exhibits a complex interaction with the dopaminergic system. It inhibits ³H-tyramine binding, a putative marker for a vesicular dopamine (DA) transporter, in striatal membranes (Kᵣ 0.5µM) and potentiates cocaine-induced dopamine release in the striatum. It also inhibits the binding of both ³H-spiperone (a D₂ receptor ligand) and ³H-SCH 23390 (a D₁ receptor ligand) to the striatum with Kᵣ values of 112 ± 9 and 532 ± 39 nM, respectively; these data suggest that flunarizine can act as a dopamine receptor antagonist.

Flunarizine most effectively inhibits the contraction of arteries and veins by depolarization, nor-
epinephrine and prostaglandin F2 in vitro in the basilar and internal carotid arteries. Given to anaesthetized dogs and cats (0.1–3 mg.kg⁻¹), it produced dose-dependent falls in blood pressure, with a reduction in vertebral, mesenteric and limb vascular resistance. The vasodilatation was most marked in the vertebral and vascular beds. Flunarizine in doses <1 mg.kg⁻¹ had no statistically significant negative inotropic effect in dogs.

Flunarizine has been reported to protect a number of tissues from injury, presumably by inhibiting calcium influx and overload. Flunarizine (in µM concentrations) inhibits shape changes (crenation) in erythrocytes and haemolysis induced by the ionophore A23187. Pre-treatment with flunarizine (0.1–3 mg.kg⁻¹) prevents citrate-induced endothelial cell desquamation and in higher doses (four doses of 5 mg.kg⁻¹) reduces the severity of isoproterenol-induced cardiac lesions and ethanol-induced gastric injury (10 mg.kg⁻¹) in rats. Flunarizine (10–40 mg.kg⁻¹) given 1–5 hours before the test has been reported to reduce brain damage in a variety of hypoxic insults in rodents.

Flunarizine (1.25–40 mg.kg⁻¹ intra-peritoneally or 0.3–5 mg.kg⁻¹ intravenously) has been demonstrated to reduce the duration, amplitude and frequency of rotational and caloric-induced nystagmus and decrease rotator-evoked potentials in rabbits. Flunarizine corrects the changes in nystagmus frequency and amplitude after vertebral compensation in labyrinthectomized guineapigs and increases blood flow in the cochlear-radiating arteriole in this species.

Flunarizine (10–40 mg.kg⁻¹) has been shown to exert an anticonvulsant effect in rodents against a variety of eleptogenic stimuli, but is particularly effective against seizures induced by electroshock. In photosensitive baboons, flunarizine (0.5–2.0 mg.kg⁻¹ intravenously) has been reported to protect against myoclonic responses to stroboscopic stimulation. Flunarizine (10 mg.kg⁻¹ and 20 mg.kg⁻¹) potentiated the efficacy of carbamazepine and valproate against maximum electroshock (50 mA)-induced seizures and, at the highest dose, enhanced that of phenytoin in mice without influencing plasma levels of these drugs.

Flunarizine exhibits some activity against histamine receptors. At doses of 0.32–0.89 mg.kg⁻¹, it has been shown to inhibit histamine-induced paw oedema and anaphylactic shock in ovalbumin-sensitized guineapigs, and 10–40 mg.kg⁻¹ intra-peritoneally inhibits histamine-induced broncho constriction.

### Pharmacokinetics

#### Absorption

Flunarizine is usually administered orally. It is rapidly and almost completely (>95%) absorbed from the gastrointestinal tract. After a single 10 mg oral dose, peak plasma levels (C max) of 50–100 µg.l⁻¹ are achieved after 2–4 hours (T max) in fasting, healthy volunteers.

#### Distribution

Following cessation of an intravenous infusion of flunarizine, plasma levels initially decline very rapidly, with half-lives of 11–19 minutes and 5–7 hours, respectively, reflecting the rate of distribution between the systemic circulation and rapidly equilibrating tissues such as the brain. Studies in vitro have shown that flunarizine is very extensively bound in blood (99%), largely to plasma proteins (90%), and to a much lesser extent to red blood cells (9%). In an individual patient, the plasma concentration is proportional to the dose. The main proteins involved in plasma binding are alpha and beta globulins. Despite extensive binding in the blood, flunarizine has a very large apparent volume of distribution, with an average value of approximately 43 l.kg⁻¹. There is considerable inter-individual variation, from 28 to 300 l.kg⁻¹. The very high volume of distribution of
flunarizine indicates that it is subject to extensive tissue binding. In keeping with the very long half-life, plasma concentrations reach the steady state after 5–6 weeks, or even longer, of repeated administration. There is considerable inter-individual variation in the steady-state plasma concentrations of flunarizine: 16% of patients had concentrations <0.02 mg.l\(^{-1}\); 24% of patients had concentrations >0.02–0.05 mg.l\(^{-1}\); 36% of patients had concentrations >0.05–0.1 mg.l\(^{-1}\); 20% of patients had concentrations >0.1–0.25 mg.l\(^{-1}\); and 4% of patients had concentrations >0.25 mg.l\(^{-1}\), probably as a consequence of variable pre-systemic metabolism. Studies in animals have shown that flunarizine achieves very high concentrations in the liver (18% of the dose), lungs and pancreas, and that it accumulates in skeletal muscle and adipose tissue. It readily crosses the blood-brain barrier, to reach concentrations in the brain 5–20 times those in plasma.

**Metabolism**

Flunarizine is subject to extensive biotransformation in the liver, with less than 0.01% of the dose being excreted unchanged in the urine over 24 hours while less than 5% is recovered unchanged in the faeces.

The steady-state concentration in different individuals is subject to fluctuations probably due to the pre-systemic metabolism, in the liver. In keeping with the very long half-life, plasma concentrations reach steady state after 5–6 weeks, or even longer, of repeated administration probably as a consequence of variable pre-systemic metabolism. The pharmacokinetics of flunarizine following repeated administration is essentially the same as those after a single dose, indicating that it is neither an inducer nor an inhibitor of its own metabolism.

Flunarizine is eliminated almost entirely by hepatic biotransformation, with less than 0.01% excreted unchanged in the urine over 24 hours and less than 5% recovered unchanged in the faeces.

The primary pathways of the oxidative metabolism of flunarizine are as below:

1. Aromatic hydroxylation at the phenyl ring of the cinnamyl moiety, resulting in 4- hydroxyl-flunarizine
2. Oxidative N-dealkylation at the 1- and 4- positions of the piperazine nitrogens, resulting in various primary and secondary metabolites.

Glucuronidation may follow the hydroxylation. *In vitro* investigations using human cDNA-expressed cytochrome enzymes indicated that CYP2D6 catalysed the aromatic hydroxylation at the phenyl ring of the cinnamyl moiety; CYP 2C9, 1A1, 1A2 and 2A6 may be involved in the N-dealkylation. CYP3A4 did not show any detectable activity in the biotransformation of flunarizine. The impact of the involvement of CYP2D6 on the *in vivo* overall metabolic clearance of flunarizine cannot be derived from these *in vitro* data, but it may contribute to the observed inter-individual variability in the steady-state plasma concentrations of flunarizine.

It is probable that the considerable inter-individual variability that occurs in the plasma concentrations of flunarizine at the steady state is a consequence of the extensive pre-systemic metabolism that the drug undergoes.

Flunarizine oxidation is induced by co-administration of carbamazepine and/or phenytoin, while flunarizine itself at therapeutic doses is not an inducer of oxidative metabolism.

**Excretion**

Flunarizine is eliminated almost entirely by hepatic biotransformation, with less than 0.01% excreted unchanged in the urine over 24 hours and less than 5% recovered unchanged in the faeces.
The metabolites are excreted largely in the faeces via the bile. The very high volume of distribution results in a long terminal elimination half-life of flunarizine, approximately 18 days following a single dose.

The total body clearance of flunarizine following oral administration, largely reflecting clearance by the liver, is approximately 120 ml.min⁻¹.

Flunarizine is excreted in breast milk. While specific information on excretion in human breast milk is not available, studies in the dog have shown that concentrations in breast milk are greater than those in the plasma.

**Special Populations**

**Geriatric**

Old age has little effect on the pharmacokinetics of flunarizine. Indeed, the half-life may even be slightly shorter than in young adults, at 7.3 ± 3.3 days.

**Indications**

- **MIGARID Tablets** are used for the prophylaxis of classic (with aura) or common (without aura) migraine.
- **MIGARID Tablets** are also used for the symptomatic treatment of vestibular vertigo owing to a diagnosed functional disorder of the vestibular system.

**Dosage And Administration**

**Migraine**

Effective doses of **MIGARID Tablets** for migraine prophylaxis have generally been 10 mg daily (at night) for patients younger than 65 years of age and at 5 mg daily for patients older than 65 years. Young patients and those with a shorter duration of disease seem to respond better. If a patient responds satisfactorily to the starting dose and if a maintenance treatment is required, the dose of **MIGARID Tablets** should be decreased so that, each week, the patient has 5 days of treatment at the same daily dose of **MIGARID Tablets** and two successive drug-free days. Even if the prophylactic maintenance treatment is successful and well-tolerated, it should be interrupted after 6 months and reinitiated only if the patient relapses.

If no significant improvement is observed after 2 months of treatment with **MIGARID Tablets** for migraine prophylaxis and paroxysmal vertigo, or after 1 month of treatment for chronic vertigo, the patient should be considered a non-responder and administration of **MIGARID Tablets** should be discontinued.

**Contraindications**

**MIGARID Tablets** are contraindicated in those individuals who are

- Hypersensitive to flunarizine or cinnarizine;
- Suffering from depressive illness;
- Have Parkinson’s disease; and
Suffering from extra-pyramidal disorders.

Relative Contraindication

• Hepatic impairment

Warnings And Precautions

General

Flunarizine may lead to drowsiness, which is aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be cautioned against driving motor vehicles or performing other potentially hazardous tasks where a loss of mental alertness may lead to accidents.

Flunarizine is not suited for aborting a migraine attack. The possible occurrence of an attack is, therefore, no reason to increase the dose of flunarizine. This treatment may give rise to extra-pyramidal and depressive symptoms and reveal Parkinsonism, especially in predisposed patients such as the elderly. Flunarizine should, therefore, be used with caution in such patients.

Potentially Life-Threatening Effects

Doses of flunarizine of 10–11.5 mg daily for periods of 1–16 months were associated with extra-pyramidal reactions in 10 patients. These included bradykinesia, rigidity, akathisia, orofacial dyskinesia, torticollis and tremor, of which elderly patients seem particularly at risk. The withdrawal of flunarizine resulted in recovery over a variable period of time (2 weeks to 6 months). However, akathisia may persist. Depression is also common feature. Epidemiological evidence suggests that patients older than 65 years, those with essential tremor, a family history of essential tremor, a history of iatrogenic extra-pyramidal effects or a history of Parkinson’s disease are more prone to flunarizine-induced Parkinsonism. Long-term therapy should be avoided in these patients. A case of erythema multiforme, occurring 1 month after treatment with flunarizine, was reported.

Extra-pyramidal motor signs (including Parkinsonism, orofacial tardive dyskinesia and akathisia) have been reported in 12 patients given flunarizine 10–40 mg daily, for a period between 3 weeks and 15 months; 11 also had mental depression. Partial or complete improvement of symptoms occurred after withdrawal of flunarizine. There have been other reports of similar effects, but the association with flunarizine has always been certain. Some researchers have commented that flunarizine is often used in patients at increased risk of depression (migraine and geriatric patients) or extra-pyramidal symptoms (geriatric patients) or that flunarizine may unmask subclinical idiopathic Parkinson’s disease.

Extra-pyramidal signs, including Parkinsonism, have also been associated with the related drug, cinnarizine. It has been suggested that such effects may be less likely to occur with cinnarizine than with flunarizine because of its shorter half-life and lower lipophilicity.

Porphyria

Flunarizine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in invitro systems.
Drug Interactions

Amiodarone

As flunarizine is a calcium channel blocker, caution should be exercised with certain drugs, although clinical experience with flunarizine is limited. Concomitant treatment of a calcium channel blocker and amiodarone has been reported to result in sinus arrest and atrioventricular block.

Hypnotics and Tranquillizers

Excessive sedation can occur when alcohol, hypnotics or tranquillizers are taken simultaneously with flunarizine.

Adenosine

With adenosine, prolonged bradycardia may occur and calcium channel blocking agents may enhance the neuromuscular blockade induced by non-depolarizing agents such as tubocurarine, but flunarizine is not contraindicated in patients who use beta-blocking agents.

Hepatic Enzyme Inducers

Hepatic enzyme inducers such as carbamazepine, phenytoin and valproate may interact with flunarizine by increasing its metabolism; an increase in the dosage of flunarizine may be required.

Sumatriptan

Flunarizine 10 mg once daily for 8 days was found to have no influence on the single-dose pharmacokinetics of sumatriptan. In addition, no significant changes in heart rate or blood pressure occurred.

Hepatic Impairment

Since flunarizine is primarily metabolized in the liver, dosage adjustments are required in hepatic impairment.

Pregnancy

The safety of flunarizine for use in human pregnancy has not been established. An evaluation of animal studies did not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, or the course of gestation or peri-natal and postnatal development.

Lactation

No data are available on the excretion of flunarizine in human breast milk. Breast-feeding should, therefore, be avoided in nursing mothers who are taking flunarizine.

Paediatric Use

Flunarizine has been used in migraine prophylaxis in the paediatric population.
Geriatric Use

Treatment with flunarizine may give rise to extra-pyramidal and depressive symptoms and reveal Parkinsonism, especially in predisposed patients such as the elderly. Therefore, it should be used with caution.

Undesirable Effects

The most common set of undesirable effects seen with flunarizine are weight gain, particularly in migrainous patients, depression, extra-pyramidal symptoms (sometimes associated with depression) and, rarely, galactorrhoea in female patients on oral contraceptives within 2 months of flunarizine treatment.

Some of the undesirable effects often seen with flunarizine include drowsiness, headache, insomnia, asthenia, depression, heartburn, nausea, dry mouth, gastralgia, constipation and diarrhoea.

Overdosage

On the basis of the pharmacological properties of the drug, sedation and asthenia may be expected to occur. A few cases of acute over dosage (up to 600 mg in one intake) have been reported and the observed symptoms were sedation, agitation and tachycardia. No specific antidote is known.

Shelf-Life

3 years

Storage And Handling Instructions

Protect from heat and light

Packaging Information

MIGARID 5 mg: Strip of 10 Tablets

MIGARID 10 mg: Strip of 10 Tablets

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MIGARID Tablets

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