PRODUCT MONOGRAPH

FLUNARIZINE

Flunarizine Hydrochloride Capsules

5 mg Flunarizine/Capsule

Selective Calcium-Entry Blocker

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PRODUCT MONOGRAPH

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Flunarizine Hydrochloride Capsules

5 mg Flunarizine/Capsule

THERAPEUTIC CLASSIFICATION

Selective Calcium-Entry Blocker

ACTIONS AND CLINICAL PHARMACOLOGY

Flunarizine hydrochloride is a selective calcium antagonist. It prevents cellular calcium overload by reducing excessive transmembrane calcium influx. Flunarizine does not interfere with normal cellular calcium homeostasis. Flunarizine also has antihistaminic properties.

The effects of flunarizine in the prophylaxis of migraine are most pronounced with regards to the reduction of the frequency of attacks. The severity of migraine attacks improves to a lesser extent, while little or no effect is seen on the duration of migraine episodes.

The pharmacokinetic parameters of orally administered flunarizine are summarized in Table 1.

Table 1: Pharmacokinetic parameters of flunarizine in healthy volunteers

	No. of Doses	Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC (ng/mL·h)	$t_{1/2\alpha}$ (h)	Cl_p (mL/min)	$t_{1/2\beta}$ (mean days) [range]
Single Dose Studies		5	30.5		133[a]	2.4		
		10	81.5		615[d]	2.8		
		20	117.0	2 - 4	1091[d]	3.6		
		30	81.6	2 - 6	1169[c]	5.5	443.7	4 [2 - 8]
Multiple Dose Studies	14	5	18.1[b]					
	14	10	38.8[b]					
	14	15	68.4[b]		1264[d]		301.2	[4 - 19]
	57	10	114.5		1678[d]			19

a Area under curve 0 to 8 hours

b Plasma concentrations at 2 hours

c Area under curve 0 to 168 hours

d Area under curve 0 to 24 hours

Flunarizine is well absorbed; peak plasma levels are attained 2 to 4 hours after oral administration in healthy volunteers. Plasma concentrations increase gradually during chronic administration of 10 mg daily, reaching a steady state level after 5 to 6 weeks of drug administration. Steady state plasma levels remain constant during prolonged treatment although there is substantial interindividual variation; plasma levels range between 39 and 115 ng/mL.

In 50 elderly patients (mean age 61 years), with intermittent claudication, long term (median 6 months) treatment with flunarizine, 10 mg per day, yielded fairly constant steady-state plasma levels albeit with considerable interindividual differences. While plasma flunarizine levels were between 50 ng/mL and 100 ng/mL in 46% of patients, individual values ranged from less than 20 ng/mL to 580 ng/mL. Flunarizine was devoid of cumulative effects as shown by repeated measurements.

As indicated by the large apparent volume of distribution (mean = 43.2 L/kg; range = 26.7-79.9 L/kg) seen after the oral administration of 30 mg in healthy volunteers, flunarizine is extensively distributed to tissues. Drug concentrations in tissues, particularly adipose tissue and skeletal muscle, were several times higher than plasma levels.

Flunarizine is 99.1% bound; 90% is bound to plasma proteins and 9% distributed to blood cells, leaving less than 1% present as free drug in the plasma water.

Flunarizine is metabolized principally through N-oxidation and aromatic hydroxylation. During a 48 hour period after a single 30 mg dose, minimal urinary (<0.2%) and fecal (<6%) excretion of flunarizine and/or its metabolites was found. This indicates that the drug and its metabolites are excreted very slowly over a prolonged period of time.

Flunarizine has a long elimination half-life of about 19 days.

Comparative Bioavailability

A standard, randomized, two-way crossover study was conducted in 28 healthy, adult, male volunteers to evaluate the relative bioavailability of single oral doses of FLUNARIZINE 5 mg Capsules and Sibelium® 5 mg Capsules. The mean pharmacokinetic parameters of these subjects are summarized in the following table.

Summary Table of the Comparative Bioavailability Data Flunarizine (Dose: 2 x 5 mg) From Measured Data			
Parameter	**Geometric Mean Arithmetic Mean (CV%)**		**Ratio of Geometric Means (%) (90% CI)**
	FLUNARIZINE	**Sibelium®†**	
AUC_{0-72h} (ng·hr/mL)	315.13 364.46 (55)	276.44 327.39 (58)	114.0 (106.7 - 121.9)
AUC_I (ng·hr/mL)	361.41 426.11 (60)	319.26 389.07 (65)	113.2 (106.2 - 120.6)
C_{max} (ng/mL)	27.28 29.09 (38)	24.63 26.38 (36)	110.7 (103.0 - 119.0)
T_{max} (hr)*	3.50 (38)	3.00 (37)	--
$t_{1/2}$ (hr)*	25.14 (53)	23.35 (68)	--

* Arithmetic means (CV %).
† Sibelium® is manufactured by Janssen Pharmaceutica, and was purchased in Canada.

INDICATIONS AND CLINICAL USE

FLUNARIZINE (flunarizine hydrochloride) is indicated for prophylaxis of migraine (with and without aura) in patients with frequent and severe attacks, who have not responded satisfactorily to other treatment and/or in whom other therapy has resulted in unacceptable side effects.

Flunarizine is not indicated for the treatment of acute attacks.

CONTRAINDICATIONS

FLUNARIZINE (flunarizine hydrochloride) is contraindicated in patients with a history of depressive illness, or with pre-existing symptoms of Parkinson's disease or other extrapyramidal disorders (See WARNINGS and ADVERSE REACTIONS).

Flunarizine is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Extrapyramidal Symptoms

Clinical studies indicate that flunarizine treatment, even at recommended doses, can produce motor disturbances in subjects who did not show previous neurological deficits. Elderly patients appear to be particularly at risk. The clinical symptoms resemble Parkinson's disease, however, they do not improve with antiparkinson medication. Experience to date suggests that in most instances the extrapyramidal symptoms tend to be reversible following discontinuation of flunarizine treatment.

Depression

Clinical studies indicate that flunarizine can, even at recommended doses, precipitate depression, mostly in younger patients.

Fatigue

In rare cases, fatigue may increase progressively during flunarizine treatment: in this event, therapy should be discontinued.

The recommended dose should not be exceeded. Patients should be followed closely and monitored at regular intervals so that extrapyramidal and/or depressive symptoms and/or fatigue may be detected early, and treatment discontinued. If the therapeutic effects diminish during treatment, flunarizine should be discontinued (for duration of treatment see also DOSAGE AND ADMINISTRATION).

PRECAUTIONS

Since sedation and/or drowsiness occur in some patients during treatment with FLUNARIZINE (flunarizine hydrochloride) (see ADVERSE REACTIONS), patients should be cautioned against activities which require alertness or rapid, precise responses (e.g. operating machinery or a motor vehicle) until the response to the drug has been determined.

Use in Pregnancy

To date, there are no data to support the use of flunarizine during pregnancy. It should therefore not be administered to pregnant women unless the anticipated benefits outweigh the potential risks.

Use During Lactation

Studies in lactating dogs have shown that flunarizine is excreted in milk. The concentration of flunarizine in milk is much greater than that in plasma. No data are available on the excretion in human breast milk. Women taking flunarizine should not breast feed.

Use in the Elderly

The safety and efficacy of flunarizine in the prophylaxis of migraine has not been established in elderly subjects.

Use in Children

The safety and efficacy of flunarizine in the prophylaxis of migraine has not been established in patients younger than 18 years of age.

Endocrine Effects

Galactorrhea has been reported in a few female patients, some of whom were also on oral contraceptives, within the first two months of flunarizine treatment. Discontinuation of flunarizine therapy resolved the galactorrhea in most cases. Flunarizine therapy caused a mild but significant elevation of serum prolactin levels while GH, LH, FSH and TSH levels did not show significant variation. Two cases of menstrual irregularities have been reported.

Drug Interactions

Evidence from therapeutic trials in epileptic patients indicates that whereas flunarizine does not affect the kinetics of phenytoin, carbamazepine and valproic acid, it does decrease the plasma levels of mephenytoin. Furthermore, steady state levels of flunarizine are reduced by coadministration of two or more anticonvulsants. This is considered to be a result of enhanced first pass metabolism of flunarizine as a consequence of liver enzyme induction by the anticonvulsant medications.

In other studies, flunarizine was shown not to affect the anticoagulant effect of warfarin sodium or the hypoglycemic effect of glibenclamide and insulin.

Excessive sedation can occur when alcohol, hypnotics or tranquilizers are taken simultaneously with FLUNARIZINE.

Use in Patients with Impaired Hepatic Function

Flunarizine is metabolised by the liver, therefore care should be exercised when flunarizine is given to patients with compromised liver function.

ADVERSE REACTIONS

In clinical trials with flunarizine hydrochloride in migraine patients, drowsiness (also described as sedation or fatigue) as well as weight gain (and/or increased appetite) occurred fairly frequently, in the order of 20 and 15%, respectively. Of 840 migraine patients, 23 (2.7%) and 9 (1.1%) required withdrawal from flunarizine therapy due to drowsiness and weight gain, respectively.

The most serious side effect encountered in migraineurs during clinical trials was depression. Of 840 migraine patients, 11 (1.3%) were withdrawn due to depression. International post-marketing experience suggests that patients between 20 and 54 years of age with a personal or familial history of depression are particularly at risk (see CONTRAINDICATIONS and WARNINGS).

Clinical experience in other indications and epidemiologic surveys suggest that extrapyramidal symptoms may develop during flunarizine therapy. Elderly patients are particularly at risk (see CONTRAINDICATIONS and WARNINGS).

Other side effects encountered in clinical trials for migraine prophylaxis included the following:

Gastrointestinal: Heartburn, nausea, emesis, gastralgia;

Central Nervous System: Insomnia and sleep change, anxiety, dizziness/vertigo;

Miscellaneous: Dry mouth, asthenia, muscle aches, skin rash.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms

On the basis of the pharmacological properties of the drug, sedation and asthenia may be expected to occur. A few cases of acute overdosage (up to 600 mg in one intake) have been reported and the observed symptoms included central nervous system effects (e.g. sedation, confusion and agitation) and cardiovascular effects (e.g. tachycardia).

Treatment

There is no specific antidote. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

DOSAGE AND ADMINISTRATION

Adults

The recommended dose is 10 mg daily (at night) for patients younger than 65 years of age. If, during this treatment, depressive, extrapyramidal or other unacceptable adverse experiences occur, administration should be discontinued. If, after 3 months of this initial treatment, no significant improvement is observed, the patient should be considered a non-responder and administration should also be discontinued.

If treatment goes beyond 6 months, patients should continue to be closely monitored for side effects, in particular CNS related events, and therapy should be discontinued at the first sign of adverse reactions (see WARNINGS).

Although there are no long-term controlled clinical trials with flunarizine, clinical experience suggests that 2 successive drug-free days per week may decrease the potential for adverse reactions. However, it should be noted that a brief interruption in therapy will not significantly reduce the exposure to FLUNARIZINE, given its long half-life (19 days).

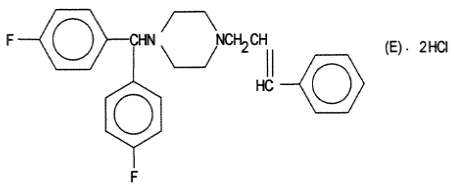
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Chemical Name: Flunarizine hydrochloride

Chemical Name: (E)-1-[bis(4-fluorophenyl)methyl]-4-(3-phenyl-2-propenyl) piperazine dihydrochloride

Structural Formula:



Molecular Formula: $C_{26}H_{26}F_2N_2 \cdot 2HCl$

Molecular Weight: 477.41

pKa: pKa_1, is about 10 and pKa_2 is about 6.

Partition Coefficient: Melting Point: Log P = 1.97 (n-octanol/water) by shake-flask method

Melting Point: 251°C

Description: Flunarizine hydrochloride is a white to pale cream coloured powder soluble in dimethylsulfoxide, PEG 400, propylene glycol, N,N-dimethylformamide or methanol. Flunarizine is poorly soluble in water or ethanol (0.1-1%).

COMPOSITION

In addition to flunarizine hydrochloride, each capsule contains the non-medicinal ingredients corn starch, stearic acid and lactose. The capsule shell, imprinted with edible black ink, contains the non-medicinal ingredients gelatin, sodium lauryl sulfate, silicon dioxide, black iron oxide, titanium dioxide, FD&C Blue #1, D&C Yellow #10, FD&C Red #40 and D&C Red #28.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15-30°C), protected from light and moisture.

AVAILABILITY OF DOSAGE FORMS

Each red and grey, size #4 capsule, imprinted "5" contains flunarizine hydrochloride equivalent to 5 mg flunarizine. Available in bottles of 60 and 100, and unit dose packages of 60 capsules.

INFORMATION FOR THE PATIENT

Please read this Information Summary carefully before taking FLUNARIZINE. You may need to read it again, so do not throw it out until you have finished your medicine.

THE NAME OF YOUR MEDICINE:

The name of your medicine is FLUNARIZINE (flunarizine hydrochloride) capsules.

FLUNARIZINE can only be obtained with a prescription from your doctor.

1) WHAT IS FLUNARIZINE FOR?

FLUNARIZINE helps prevent migraine attacks.

2) IMPORTANT POINTS TO NOTE BEFORE TAKING YOUR MEDICINE:

As with all medicines, there are important issues to consider before using FLUNARIZINE.

When not to take FLUNARIZINE

Do not take FLUNARIZINE if you have suffered or are now suffering from:
- depression;
- Parkinson's disease.

Do not take this product if you know you are allergic to the product or its ingredients. If you suspect you are allergic to this product or any of its ingredients consult your doctor or pharmacist and ask for a complete list of ingredients. If in doubt, check with your doctor before taking FLUNARIZINE.

Warnings

In a small proportion of patients, depression may occur during treatment with FLUNARIZINE, especially in younger patients who have experienced depression previously. Older people may experience slow movements, stiffness and other symptoms similar to those of Parkinson's disease. If you experience any of these, consult with your doctor. Although it seldom happens, you may experience a tired feeling that increases as the treatment with FLUNARIZINE continues. If so, contact your doctor.

Pregnancy
If you are pregnant, or think you are, you should tell your doctor, who will decide if you can take FLUNARIZINE.

Breastfeeding
Do not breastfeed if you are taking FLUNARIZINE. Consult your doctor in that case.

Other conditions
If you ever had a disease of the liver, discuss with your doctor before taking FLUNARIZINE.

Driving and operating machinery
You may get sleepy with FLUNARIZINE, especially at the beginning of treatment. Do not drive or operate machinery until you are sure that you are not drowsy.

Other medicines and alcohol
If you are taking FLUNARIZINE, alcohol, sleeping pills and tranquilizers can make you sleepy and drowsy faster. You should limit the amount of alcohol you drink and only take sleeping pills or tranquilizers if your doctor prescribes them along with FLUNARIZINE.

Medical supervision
While you are taking FLUNARIZINE, stay in touch with your doctor.

3) HOW TO TAKE FLUNARIZINE AND HOW MUCH
It may take FLUNARIZINE some time to work, often several weeks. Your doctor will tell you how long you need to take FLUNARIZINE.

Swallow the capsules with water.
Never take more than the number of capsules you are supposed to.

- Starting FLUNARIZINE treatment: If you are under 65 years of age, take 2 capsules (10 mg) every day before going to bed. - Continuing with FLUNARIZINE: After 3 months, your doctor will tell you whether you should continue with FLUNARIZINE. If you take FLUNARIZINE for more than 6 months, you should pay periodic visits to your doctor.

4) UNDESIRED EFFECTS

Some patients may feel sleepy or tired, but these effects generally go away spontaneously. If they do not, and they give you a lot of trouble, contact your doctor.

Weight gain (and/or increased appetite) is sometimes experienced, so try not to eat more than you usually do.

During treatment, depression sometimes occurs, especially in women who have experienced depression previously. Older people may experience slow movements or stiffness. Also, restlessness, trembling or uncontrolled movements of the face or the arms and legs may occur. If any of these happen, check with your doctor.

Inform your doctor or pharmacist promptly about any other unwanted effects that you experience.

5) OVERDOSE

Contact either your doctor, hospital emergency department or the nearest poison centre immediately if you have taken too much FLUNARIZINE. You may experience sleepiness, tiredness or, with very large amounts, agitation or a fast heartbeat.

6) HOW TO STORE FLUNARIZINE

Keep FLUNARIZINE at room temperature (between 15 and 30°C), protected from light and moisture (do not store it in the bathroom, for example).

Do not use FLUNARIZINE after it has expired (as indicated in the label), even if it has been stored properly. (It is a good idea to return old medicine to your pharmacist.)

7) WHAT IS IN FLUNARIZINE?

The active ingredient in FLUNARIZINE is flunarizine. FLUNARIZINE comes as red-and-grey capsules. One capsule contains 5 milligrams of flunarizine (as flunarizine hydrochloride).

8) A REMINDER

This medicine has been prescribed by your doctor for you. Use it only as directed. Do not give FLUNARIZINE to someone else, even if his/her symptoms are similar to yours. Keep this and other medications out of the reach of children.

9) ADDITIONAL INFORMATION

If you have additional questions on your medication, consult with your doctor or pharmacist. Always inform your doctor or pharmacist if you are using other medicines because some drugs should not be taken together.

PHARMACOLOGY

Flunarizine is a difluorinated derivative of cinnarizine which acts as a selective calcium-entry blocker.

A) Receptor-Binding Studies

In *in vitro* receptor-binding assays, flunarizine showed moderate binding affinity for five receptor sites in the following order of potency (Ki nM): histamine-H_1(68), dopamine-D_2 (80), serotonin-S_2(200), α_1-adrenergic (250), nitrendipine calcium sites (380). Flunarizine was inactive at the serotonin-S_1, muscarinic-cholinergic, α_2-adrenergic, and β-adrenergic receptor sites.

In *ex vivo* receptor-binding studies, flunarizine occupied the midbrain histamine-H_1 receptor sites in a dose-related manner (minimal effective dose: 1.25 mg/kg) and for a prolonged period of time. Dopamine-D_2 receptor sites in the striatum were occupied only at higher doses (10 mg/kg) and for a brief period of time. Serotonin-S_2, α_1-adrenergic and ^{3}H-nitrendipine binding sites did not become significantly occupied in doses up to 10 mg/kg.

B) Calcium-Mediated Cell Changes

Flunarizine exerted a protective effect against various calcium-mediated cell changes. *In vitro,* flunarizine inhibited the discocyte to echinocyte transformation of human RBC induced by ionophor A 23187 in the presence of calcium. Pretreatment with IV flunarizine also prevented the increased endothelial cell permeability brought about by weak electrical stimulation in the rabbit carotid artery. Finally, oral flunarizine prevented histamine, serotonin, bradykinin or arachidonic acid-induced changes in microvascular permeability in the rat skin.

C) Flunarizine in Experimentally-Induced Hypoxia/Anoxia

The lethal effect of KCN in rats was prevented by orally administered flunarizine (ED_{50}: 12 mg/kg). KCN-induced lethality involves respiratory failure at the CNS level. However, low-dose KCN-induced hyperventilation, mediated by chemoreceptors in peripheral arteries, remained unaffected. The results suggest that flunarizine protects against the anoxic effects of the cyanide ion in brain tissue and that the drug demonstrates a specificity for the CNS.

Cerebral ischemia, induced in rats by transient 4-vessel occlusion, resulted in considerable damage to the CA_1, pyramidal cell layer of the hippocampus. Flunarizine, given as a postischemic treatment (IV 2-min before re-circulation and PO during 3 days of recovery) limited the structural damage. This observation was supported by *in vitro* studies in which flunarizine (10^{-7}M) protected isolated hippocampal slices from the effects of hypoxia.

Survival rates in mice, after carotid artery ligation, increased significantly in flunarizine-pretreated animals. The minimal effective dose, which brought about significant protection, was 2.5 mg/kg IP with drug effect being exerted up to 24 hours.

Survival rates were also evaluated in rats exposed for 1 minute to pure nitrogen. While none of the control animals survived, flunarizine protected the rats, the ED_{50} being 14.0 mg/kg PO when given 4 hours prior to exposure.

The effect of flunarizine on ischemia-induced EEG and cerebral blood flow changes was evaluated in dogs. Incomplete ischemia was achieved by repeated occlusion of the left subclavian and brachiocephalic arteries. Cortical temperature was taken as a qualitative measure of tissue perfusion. In control animals, cortical temperature diminished progressively with each occlusion and failed to return to baseline following re-perfusion. In flunarizine-treated dogs (0.1 mg/kg IV prior to the first occlusion), cortical temperature changed only slightly. The difference between vehicle and flunarizine-treated dogs was highly significant. The EEG changed towards slow theta and delta waves with a progressive flattening in control dogs while its functioning was preserved in the flunarizine-treated animals.

D) <u>Cardiovascular effects</u>

The effects of flunarizine on phenylephrine (PhE) and norepinephrine (NE)-induced vasoconstriction were examined in the isolated perfused rat mesentery. Both agents produced vasoconstriction in a dose-related manner. In flunarizine-pretreated rats (3 mg/kg IV), the dose-response curves were shifted to the right indicating that flunarizine exerted an anti-vasoconstrictor effect. When flunarizine was added to the perfusion medium, the vasoconstrictor responses to both PhE and NE were attenuated. Neither agent produced vasoconstriction in a calcium-free environment.

Flunarizine, 5 mg/kg IV, did not affect blood pressure, heart rate and cardiac output in anesthetized rats. However, it significantly decreased renal and splenic blood flow. The changes in blood flow were associated with similar changes in the percent distribution of cardiac output to these organs. Blood flow to other organs, namely the heart, liver, brain, lungs, and mesentery remained unchanged indicating that flunarizine influenced local regulatory mechanisms.

Flunarizine was also administered to anesthetized dogs, at doses ranging from 0.16 to 5.0 mg/kg IV. The lowest dose was without effect. The 0.63 mg/kg dose significantly decreased dp/dt and right ventricular force while blood pressure, heart rate and left ventricular pressure remained unchanged. At higher doses, all parameters decreased in a dose-related manner.

Although left ventricular dp/dt decreased, cardiac index and coronary artery blood flow increased indicating that myocardial pump performance was not impaired by flunarizine in doses up to 2.5 mg/kg IV.

TOXICOLOGY

Acute Toxicity

Route of Administration	Species	Sex	Duration of Observation (days)	LD_{50} (mg/kg)
i.v.	Mice	M F	14 14	31* 34*
i.v.	Rat	M & F	14	>22*
i.v. infusion	Rat	M & F	14	>25*
intra-arterial	Rat	M & F	14	>24*
i.p.	Mice	M F	7 7	174 142
i.p.	Rats	M F	7 7	353 312
oral	Mice	M F	7 7	815 >1280
oral	Rats	M F	7 7	312 247
oral	Guinea-pigs	M F	7 7	640* 300
i.p.	Mice	M F	7 7	468 501
i.p.	Rats	M & F	7	>600
s.c.	Mice	M & F	7	>6000
s.c.	Rats	M & F	7	>1000
oral	Mice	M F	7 7	1928 1863
oral	Rats	M F	7 7	>3000 871

* indicates approximate value

Behavioral, neurological and autonomic symptomatology observed during the acute toxicity studies:

Intravenous Administration

Mice: exophthalmos, hypotonia, tremors, dyspnea, convulsions, loss of righting reflex, occasional inflammation at injection site
Rats: hypotonia, ataxia, catalepsy, loss of righting reflex, palpebral ptosis, dyspnea, occasional inflammation at injection site
Rats (infusion): some cyanosis followed by necrosis at injection site
Rats (intra-arterial): hypotonia, hypothermia, piloerection, tremors and loss of righting reflex, paresis followed by hindpaw necrosis of cannulated leg

Oral Administration

Mice: piloerection, exophthalmos, tremors, convulsions, abnormal breathing
Rats: piloerection, ptosis, ataxia, abnormal gait, tremors, abnormal breathing, diarrhea
Guinea-pigs: ptosis, ataxia, tremors, convulsions

Intraperitoneal Administration

Mice: decreased spontaneous activity, ataxia, tremors, convulsions, ptosis, hypothermia, abnormal breathing, diarrhea
Rats: sedation, hypotonia, ataxia, catalepsy, convulsions, ptosis, hypothermia, abnormal breathing and cyanosis, diarrhea

Subcutaneous Administration

Mice: decreased activity, piloerection, ptosis, abnormal breathing, diarrhea, loss of hair
Rats: decreased activity, piloerection, abnormal breathing, loss of hair

Subacute Toxicity

Oral Toxicity Study in Wistar Rats (13 weeks): Groups of 10 male and 10 female Wistar rats were administered flunarizine in the diet at doses of 0, 5, 20 or 80 mg/100 g food. The actual daily doses were 4.5, 18.1 and 72.3 mg/kg. There was no mortality in any of the groups or behavioural changes in the low- and medium-dose animals. High-dose animals exhibited sedation, rough coats, back arching and poor general condition during the early part of the study. Food consumption was reduced dose-dependently; the reduction was slight in males and substantial in females. Body weight gain was reduced in a corresponding fashion.

There were no effects on hematology or urinalysis with the exception of occasional granular casts in the urine of some high-dosed rats. The following significant changes were observed in serum biochemistry: decreased potassium in mid-and high-dose females and all treated males; decreased chloride in mid- and high-dose females; increased CO_2 in the mid- and high-dose females; increased alkaline phosphatase in high-dose females; elevated bilirubin in all treated females; elevated SGOT in the high-dose females, and decreased haptoglobin in all treated females.

The only gross pathological differences were filiform uteri and ovarian follicular enlargements in mid- and high-dose females. Relative brain weights were increased in mid- and high-dose groups and relative liver weights were increased in high-dose animals. Absolute adrenal weights were significantly decreased in mid- and high-dose females. Relative gonad weights were increased in mid- and high-dose males while absolute gonad weights were decreased in high-dose females. Histological findings included vacuolated neurons in the colliculus or thalamus and/or nucleus reticularis of some rats in all groups including one control animal.

The livers showed centrilobular cloudy swelling and/or granular to vacuolar degeneration with slight fatty surcharge in high-dose rats. In the mid-dose animals similar but weaker changes were noted. The kidneys of the high-dose rats showed more or less marked degenerative changes of the tubuli recti and Henle's loops.

Oral Toxicity Study in Beagle Dogs (3 months): Flunarizine was administered daily for 3 months in gelatin capsules to 3 beagle dogs/sex/dose at the following doses (mg/kg): 4.2 from day 1-77 and 8.5 from day 78-91 (low-dose); 12.7 from day 1-21 and 16.9 from day 22-91 (mid-dose) and 38.1 from day 1-21, 50.8 from day 22-44, 38.1 from day 45-77 and 50.8 from day 78-91. Miosis and emesis occurred in the mid- and high-dose groups. High-dose animals also exhibited gingival swelling, relaxation of the nictitating membrane, ataxia, tremors, muscle tension, prostration, myoclonus and side to side head movement. There were no effects on food consumption and substantial weight loss occurred in only one high-dose female dog.

Hematology and urinalysis were normal. There was a decrease in serum potassium and chloride and increase in serum CO_2 in high-dose dogs and a dose-related increase in alkaline phosphatase in 2 mid- and 4 high-dose dogs. Serum electrophoretic studies indicated decreases for albumin, which became significant in the high-dose group.

Tachycardia associated with lower blood pressure occurred in all groups and was accompanied by ST segment deviation and T wave changes in high-dose animals. Gross pathology and histopathology reflected gingival hyperplasia in mid-and high-dose dogs.

Chronic Toxicity

Oral Toxicity Study in Wistar Rats (6 and 12 months): Flunarizine was administered in the diet at dosages of 0, 5, 20 or 80 mg/100 g of food to groups of 10 male and 10 female Wistar rats for 6 or 12 months. The actual daily doses were 3.8, 15.4 and 65.0 mg/kg flunarizine. Several of the rats died or had to be sacrificed in a moribund state, namely: 30% of high-dose females in the 6-month study; 40% of the high-dose males and 60% of high-dose females in the 12-month study. One control male and one low-dose female also died in the latter study. High-dosed animals exhibited sedation and catalepsy during the entire experimental period. Sedation was less pronounced at the lower doses. Food consumption was reduced in the low- and high-dose males at 6 months, and in most females at both 6 and 12 months. Body weight gain was decreased in mid- and high-dose females in both studies.

Hematology findings included: decreased eosinophils in high-dose males at 6 months; increased WBC in high-dose females at 6 months and increased hematocrit and hemoglobin in high-dose females at 12 months. Biochemical findings included: increased alkaline phosphatase in high-dose females at 6 months; decreased potassium in all animals at 12 months with practically all values being below the normal range; decreased calcium in all females, and decreased phosphorus in high-dose males at 12 months. Urinary creatinine was decreased in the mid- and high-dose females at 6 and 12 months.

Gross pathology was normal except for an increased frequency of malformed incisors in high-dose females at both 6 and 12 months, and an adenofibroma of the mammary glands (confirmed histologically) in a low-dose female rat at 12 months. Relative liver weights were increased at 6 and 12 months in the high-dose groups with the values being outside of the normal ranges. Relative kidney weights in mid- and high-dose males and females, and relative brain weights in mid- and high-dose females were increased at 6 and 12 months. Absolute and relative adrenal weights were increased in high-dose males at 6 months. Histopathological changes were seen mainly in high-dose rats, the changes observed at the lower doses were minor and occurred only occasionally. The following lesions were seen: the lungs of some rats showed septal cell proliferation, which on occasion lead to lipoid pneumonia; the liver showed centrilobular swelling and vacuolization

(fatty degeneration), as well as hyaline degeneration (only at 12 months); female rats showed evidence of prolonged diestrus, i.e.: reduced number of *corpora lutea* and increased clear glandular tissue of the ovaries, and atrophy of few uteri. Changes related to prolonged diestrus were also observed in mid-dose females at 6 months. The zona glomerulosa and on occasion the zona fasciculata of the adrenals were thickened and the fatty load increased; gingivitis and deficient calcification of dentin and of alveolar bone were seen in many rats, particularly females.

Oral Toxicity Study in Beagle Dogs (12 months): Flunarizine was administered 6 days/week for 52 weeks in gelatin capsules to three beagle dogs/sex/group at doses of 0, 5, 20, 40 or 80 (reduced to 40 after 2 weeks) mg/kg/day. Only 1 female dog survived in the 40-80 mg/kg group. Two males in the 20 mg/kg group and one female in the 40 mg/kg group died. In the mid- and high-dose animals salivation, emesis, prostration and occasional tremors were observed. All survivors showed an increase in body weight although this was slightly and substantially less in mid- and high-dose dogs, respectively, when compared to controls. Blood pressure was slightly decreased in mid- and high-dose animals and there was a dose-related increase in pulse rate in treated animals.

Hematology was normal in low- and mid-dose animals. There was a decrease followed by a terminal increase in WBC; non-segmented heterophils, lymphocytes and monocytes increased and normoblasts appeared in the high-dose group. Blood chemistry and urinalysis findings were normal.

Surviving dogs at 12 months showed no changes in gross pathology except the high-dose group which exhibited gingival hypertrophy and increased dental calculus. Withdrawal of the drug during 17 weeks, did not completely reverse the hyperplastic changes in the gum. Dogs which died during the study had empty digestive tracts with congestion of gastric and duodenal mucosa, swollen gums and tartar on the teeth. In the animals which died, agonal and autolytic lesions were observed.

Carcinogenicity Studies

Carcinogenicity Study in Albino Swiss Mice (18 months): Four groups of 50 male and 50 female Albino Swiss mice received flunarizine in the diet, at doses of 0, 5, 20 or 40 mg/kg/day for 18 months. In male animals, mortality was 38%, 50%, 28% and 26% in the control, low, medium and high-dose groups, respectively. In female animals, mortality was 32%, 38%, 62% and 90% in the control, low, medium and high-dose groups, respectively.

The mortality in the medium and high-dose groups was significantly higher than that seen in the control group.

Gross pathological examination revealed mammary gland stimulation in the medium- and high-dose females and an increase in mammary adenocarcinomas in all the treated female mice with the increased incidence being significant at the 20 mg/kg dose level. There were no other significant differences between control and treated mice and it was concluded that the effect on mammary gland tissue was probably due to a weak dopamine antagonistic effect.

Carcinogenicity Study in Wistar Rats (24 months): Four groups of 50 male and 50 female Wistar rats received flunarizine in the diet, at doses of 0, 5, 20 or 40 mg/kg/day for 24 months. The high-dose (40 mg/kg) groups were treated with 80 mg/kg for the first 2 months. Survival rates were extremely low both in control and treated groups. More than 90% of the male rats and about 80% of the female rats died in the course of the study. While flunarizine did not affect tumor rate or type in rats at the doses studied, the validity of the study is questionable in view of the high mortality.

Mutagenicity

Flunarizine had no mutagenic effects when tested by the Ames Test, the sister chromatid change test in human lymphocytes, the sex-linked recessive lethal test in Drosophila melanogaster, the micronucleus test in male rats or the dominant lethal test in male and female mice.

Reproduction And Teratology Studies

Fertility and General Reproductive Performance in Wistar Rats: Three hundred twenty Wistar rats were divided into groups of 20 males and 20 females. Flunarizine, 0, 10, 40 or 160 mg/100 g food, (approximately 0, 10, 40 and 160 mg/kg) was administered at each dosage level to males for 60 days pre-mating or to females for 14 days pre-mating and 21 days of gestation. Treated animals were mated with non-treated animals. In dosed females, there were no pregnancies at the 160 mg/kg dose and 14/20 animals died. Two of the 160 mg/kg dosed males also died. All other animals survived until the end of the study. In female rats, treated with 40 mg/kg of flunarizine, the following changes were seen: decreased weight gain during pregnancy, decreased rate of pregnancy (50%), increase in the number of resorbed fetuses (51%), decreased litter size and decreased weight of pups at birth. The low dose of flunarizine had no effect on any of the parameters evaluated. In non-dosed females, mated with treated males, only a slight elevation of resorption was seen at the highest dose.

Teratology Study in Wistar Rats: Groups of 20 female Wistar rats received flunarizine 0, 10, 20 or 40 mg/100 g food (approximately 0, 10, 20 and 40 mg/kg) from day 6 to day 15 of pregnancy. Two females died in the high-dose group. Pregnancy rates at day 22 post-mating were 95% (0 mg/kg), 90% (10 mg/kg), 85% (20 mg/kg) and 56% (40 mg/kg). Litter size, live fetuses and number of resorptions were comparable in the 0, 10, and 20 mg/kg groups. At the 40 mg/kg dose, the resorption rate was slightly increased (16.4% vs. 6.0%) and number of live fetuses slightly decreased (84% vs. 94%) when compared to controls. There was no evidence of teratogenicity.

Teratology Study in New Zealand Rabbits: Groups of 20 female New Zealand rabbits received flunarizine by gavage at doses of 0, 2.5 or 10 mg/kg from day 6 to day 18 of pregnancy. One female in each of the flunarizine-treated groups died. After artificial insemination, the pregnancy rates were 65%, 90% and 85% in the control, 2.5 mg/kg and 10 mg/kg groups respectively. The percentages of resorptions increased with increasing dose from 7.8% in the control group to 13.5% in the 2.5 mg/kg group and 28.6% in the 10 mg/kg group. The number of live births decreased correspondingly, the values being 89.6%, 84.8% and 71.4% in the control, low-dose and high-dose groups, respectively. There was no evidence of teratogenicity.

Perinatal and Postnatal Study in Wistar Rats: Groups of 20 female rats received flunarizine, 0, 10, 20 or 40 mg/100 g food (approximately 10, 20 and 40 mg/kg) from day 16 of pregnancy throughout a 3-week lactation period. Body weight gain and food consumption showed dose-related decreases. Litter size (8.5 vs. 9.9) and the percentage of live fetuses (62.3% vs. 93.9%) were lower in the 40 mg/kg group than in the control group. There were no teratogenic effects. At weaning the survival rates were 94% in control dams, 66% at 10 mg/kg, 10% at 20 mg/kg and 1.9% at 40 mg/kg. The decreased survival rates were probably due to a dose-related decrease in food consumption and milk production in the treated females.

Other Endocrine Studies

Effect of flunarizine on the female genital tract and mammary gland in mice: Groups of 20 female mice received flunarizine in the diet at approximate doses of 0, 5, 20 or 40 mg/kg for 8 days. The following dose-related changes were seen in mice treated with 20 or 40 mg/kg flunarizine: slightly increased acinar growth of the mammary glands, pseudopregnant-stage of the vagina, pseudopregnant *corpora lutea* in the ovaries and decreased diameter of the uterine horns. In mice treated with the 5 mg/kg dose, all these parameters were similar to those seen in control animals.

Effect of flunarizine on the estrus cycle in rats: Flunarizine was administered by gavage to young female rats, with regular, 4-day cycles 24 hours after detection of estrus. The potential

prolongation of the diestral period was evaluated by daily vaginal smears. Up to 5 mg/kg, flunarizine did not affect normal cycling. At 10 mg/kg, flunarizine delayed the cycle by one day while at 20 mg/kg it caused pseudopregnancy.

REFERENCES

1) Benvenuti F, Baroni A, Bandinelli S, Ferrucci L, Corradetti R, Pantaleo T. Flunarizine-induced Parkinsonism in the elderly. J Clin Pharmacol 1988; 26: 600-608.

2) Bono G, Manzoni GC, Martucci N, et al. Flunarizine in common migraine: Italian cooperative trial. II. Long-term follow-up. Cephalalgia 1985; 2: 155-158.

3) Greenberg DA. Calcium channel antagonists and the treatment of migraine. Clin Neuropharmacol 1986; 9: 311-328.

4) Holmes B, Brogden RN, Heel RC, Speight TM and Avery GS. Flunarizine: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. Drugs 1984; 27: 6-44.

5) Kapetanovic IM, Torchin CD, Kupferberg HJ, et al. Pharmacokinetic profile of flunarizine after single and multiple dosing in epileptic patients receiving comedication. Epilepsia 1988; 29: 770-774.

6) Lucking CH, Oestreich W, Schmidt R, Soyka D. Flunarizine vs. propranolol in the prophylaxis of migraine: Two double-blind comparative studies in more than 400 patients. Cephalalgia 1988; 8 (suppl 8): 21-26.

7) Lugaresi A, Montagna P, Gallassi R, Lugaresi E. Extrapyramidal syndrome and depression induced by flunarizine. Eur Neurol 1988; 28: 208-211.

8) Manzoni GC, Bono G, Sacquegna T, Manna V, et al. Flunarizine in common migraine: Italian cooperative trial. I. Short-term results and responders' definition. Cephalalgia 1985; 2: 149-153.

9) Mendenapoulous G, Manafi TH, Logothetis I, Bostantjopoulou S. Flunarizine in the prevention of classical migraine: a placebo-controlled evaluation. Cephalalgia 1985; 5: 31-37.

10) Micheli F, Pardal MF, Gatto M, et al. Flunarizine and cinnarizine-induced extrapyramidal reactions. Neurology 1987; 37: 881-884.

11) Pini LA, Ferrari A, Sternieri E. Influence of prolonged therapy with flunarizine on glucose, insulin and C-peptide metabolism. Pharmacol Res Commun 1988; 20: 633-634.

12) Rascol A, Montastruc JL, Rascol 0. Flunarizine versus pizotifen: A double-blind study in the prophylaxis of migraine. Headache 1986; 26: 83-85.

13) Solomon GD. Comparative efficacy of calcium antagonist drugs in the prophylaxis of migraine. Headache 1985; 25: 368-371.

14) Spierings ELH, Messinger HB. Flunarizine vs. pizotifen in migraine prophylaxis: a review of comparative studies. Cephalalgia 1988; 8 (suppl 8): 27-30.

15) Steardo L, Marano E, Baron P, et al. Prophylaxis of migraine attacks with a calcium-channel blocker: flunarizine versus methysergide. J Clin Pharmacol 1986; 26: 524-528.

16) Van Neuten JM. Vascular pharmacology of calcium entry blockers. In: Calcium Entry Blockers in Cardiovascular and Cerebral Dysfunctions. Godfraind T, Herman AG and Wellens D. Eds. Martinus Nijhoff Publishers 1984; 59-72.

17) Van Nueten JM, Wauquier A, Van de Clerck F, Van Reempts J. Vascular reactivity of selective calcium entry blockers. Proceedings of the 5th International Meeting on Atherosclerosis and Cardiovascular Diseases. Bologna, Italy, November 28-30, 1983.

18) Wauquier A, Ashton D, Edmonds HL. Protection against cerebral hypoxia by anti-migraine drugs. In: The Pharmacological Basis of Migraine. Amery W, Van Neuten J and Wauquier A., Eds. Pitman, London, 1984.

19) Product Monograph. Sibelium® (Flunarizine Hydrochloride Capsules 5 mg) -Selective Calcium-Entry Blocker. Pharmascience Inc., September 1, 1998.