For the use of a Registered Medical Practitioner or a Hospital or Laboratory

Rx

Flunarizine Dihydrochloride Tablets I.P.

Sibelium® 5 mg
Sibelium® 10 mg

DOSAGE FORMS AND STRENGTHS

5 mg tablets

A white to off white round, flat, beveled edge, uncoated, circular tablets having 'S' inscription on one side and plain on other side. Each tablet contains Flunarizine Dihydrochloride I.P. equivalent to Flunarizine 5 mg.

10 mg tablets

A white to off white round, flat, beveled edge, uncoated, circular tablets having 'S' inscription on one side and break line on other side. Each tablet contains Flunarizine Dihydrochloride I.P. equivalent to Flunarizine 10 mg.

For excipients, see Section List of Excipients.

CLINICAL INFORMATION

Indications

Prophylaxis of classic (with aura) or common (without aura) migraine.
Symptomatic treatment of vestibular vertigo, due to a diagnosed functional disorder of the vestibular system.

Dosage and Administration

Adults and elderly (18 years of age and older)

- **Migraine prophylaxis**

Starting dose

Treatment is started at 10 mg daily (at night) for adult patients aged 18 to 64 years and at 5 mg daily for elderly patients 65 years and older. If, during this treatment, depressive, extrapyramidal or other unacceptable adverse experiences occur, administration should be discontinued *(see Warnings and Precautions and Adverse Reactions)*. If, after 2 months of this initial treatment, no significant improvement is observed, the patient should be considered a non-responder and administration should be discontinued.

Maintenance treatment

If the patient responds satisfactorily and if a maintenance treatment is needed, the dosage schedule should be changed so that each week the patient receives 5 days of treatment at the same daily dose and 2 successive drug-free days.

Even if the prophylactic maintenance treatment is successful and well tolerated, it should be interrupted after 6 months and re-initiated only if the patient relapses.

- **Vertigo**

The same daily doses should be used as for migraine, but the starting treatment should not be given longer than needed for symptom control, which generally takes less than 2 months.

If, however, no significant improvement is observed after one month for chronic vertigo or after 2 months for paroxysmal vertigo, the patient should be considered a non-responder and administration should be discontinued.

Special populations

Pediatrics (6 to 17 years of age) – migraine prophylaxis

- The recommended dose is 5 mg daily (at night).
- The dose may be increased to 10 mg daily in patients weighing over 40 kg, if required.

If, during this treatment, depressive symptoms or other unacceptable adverse experiences occur, administration should be discontinued (see *Warnings and Precautions* and *Adverse Reactions*). If, after 3 months of this initial treatment, no significant improvement is observed, the patient should be considered a non-responder and administration should be discontinued.

The maximum recommended treatment duration is 6 months.

Pediatrics (5 years of age and younger) – migraine prophylaxis

The safety and efficacy of Sibelium for prophylaxis of migraine in pediatric patients aged 5 years and younger have not been established.

Pediatrics (17 years of age and younger) – vertigo

The safety and efficacy of Sibelium for treatment of vertigo in pediatric patients have not been established.

Contraindications

Sibelium 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 Precautions and Adverse Reactions*).

Hypersensitivity to flunarizine or to any of the excipients.

Warnings and Precautions

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

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

The recommended dose should not be exceeded. Patients should be seen at regular intervals, especially during maintenance treatment, so that extrapyramidal or depressive symptoms may be detected early and if so, treatment discontinued. If, during maintenance treatment, the therapeutic effects wane, treatment should also be discontinued (*see Dosage and Administration*).

Interactions

Excessive sedation can occur when alcohol, hypnotics or tranquillisers are taken simultaneously with Sibelium.

Sibelium is not contraindicated in patients who use beta blocking agents.

The pharmacokinetics of flunarizine were unaffected by topiramate. During co-administration of Sibelium with topiramate 50 mg every 12 hours, a 16% increase in the systemic exposure to flunarizine in migraine patients was observed comparable to a 14% increase in patients treated with flunarizine only. The steady-state pharmacokinetics of topiramate were unaffected by flunarizine. Chronic administration of flunarizine did not affect the disposition of phenytoin, carbamazepine, valproate or phenobarbital. Plasma concentrations of flunarizine were generally lower in patients with epilepsy taking these anti-epileptic drugs (AEDs) compared to healthy subjects given similar doses. The plasma protein binding of carbamazepine, valproate, and phenytoin is not affected by co-administration with flunarizine.

Pregnancy and Breast-feeding

Pregnancy

The safety of Sibelium for use in human pregnancy has not been established.

An evaluation of animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or fetus, the course of gestation or peri- and postnatal development.

Breast-feeding

Breast-feeding should be discouraged in women taking Sibelium. Studies in lactating dogs have shown that flunarizine is excreted in the milk and that the concentration in the milk is greater than in the plasma. No data are available on the excretion in human breast milk.

Effects on Ability to Drive and Use Machines

Since somnolence may occur, especially at the start of the treatment, caution should be exercised during activities such as driving or operating dangerous machinery.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of flunarizine dihydrochloride based on the comprehensive assessment of the available adverse event information. A causal relationship with flunarizine dihydrochloride cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

Placebo-controlled double-blind data – adverse reactions reported at ≥1% incidence

The safety of Sibelium (5 to 10 mg/day) was evaluated in 500 subjects (of which 247 were treated with Sibelium, 253 were given placebo) who participated in two placebo-controlled, double-blind parallel clinical trials, one in the treatment of migraine and the other in the treatment of vertigo.

Adverse Reactions reported by ≥1% of Sibelium-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Reactions Reported by ≥1% of Sibelium-Treated Subjects in 2 Double-Blind Parallel Placebo-Controlled Clinical Trials of Sibelium

System/Organ Class Adverse Reaction	**SIBELIUM (5-10 mg)** **(n=247)** **%**	**Placebo** **(n=253)** **%**
Infections and Infestations		
Rhinitis	4.0	1.6
Metabolism and Nutrition Disorders		
Increased appetite	4.0	2.0
Psychiatric Disorders		
Depression	4.5	0.8
Nervous System Disorders		
Somnolence	9.3	1.2
Gastrointestinal Disorders		
Constipation	2.4	0.4
Musculoskeletal and Connective Tissue Disorders		
Myalgia	2.4	0.8
Reproductive System and Breast Disorders		
Menstruation irregular	2.8	1.2
Breast pain	1.2	0.4

Investigations		
Weight increased	11.3	2.8

Active comparator-controlled data – adverse reactions reported at ≥1% incidence

Two double-blind active comparator-controlled trials were selected to determine the incidence of adverse reactions. In these two studies, 476 subjects were treated with 10 mg/day Sibelium, one in the treatment of migraine and the other in the treatment of vertigo or migraine.

Adverse reactions reported by ≥1% of Sibelium-treated subjects noted in the active-comparator controlled clinical trials and not listed in Table 1 are shown in Table 2.

Table 2. Adverse Reactions Reported by ≥1% of Sibelium-Treated Subjects in 2 Double-Blind Active Comparator Clinical Trials of Sibelium

System/Organ Class Adverse Reaction	**SIBELIUM (10 mg/day)** **(n=476)** **%**
Gastrointestinal Disorders	
Abdominal pain upper	2.3
General Disorders and Administration Site Conditions	
Fatigue	2.9

Placebo- and active comparator-controlled data – adverse reactions reported at <1% incidence

Additional adverse reactions that occurred in <1% of Sibelium-treated subjects in either of the above two clinical datasets are listed in Table 3.

Table 3. Adverse Reactions Reported by <1% of Sibelium-Treated Subjects in Either the Placebo- or Comparator-Controlled Clinical Trials

Psychiatric Disorders
Depressive Symptom
Sleep disorder
Apathy
Nervous System Disorders
Torticollis
Tinnitus
Lethargy
Paraesthesia
Sluggishness
Restlessness
Coordination Abnormal

Disorientation

Cardiac Disorders

Palpitations

Gastrointestinal Disorders

Intestinal obstruction

Gastrointestinal disorder

Dry Mouth

Skin and Subcutaneous Tissue Disorders

Hyperhidrosis

Musculoskeletal and Connective Tissue Disorders

Muscle Spasms

Muscle Twitching

Reproductive System and Breast Disorders

Oligomenorrhoea

Menorrhagia

Hypertrophy Breast

Menstrual Disorder

Libido Decreased

General Disorders and Administration Site Conditions

Generalized Edema

Asthenia

Edema Peripheral

Post-marketing Data

Adverse events first identified as adverse reactions during post-marketing experience with Sibelium are included in Tables 4. In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports
Not known	the frequency cannot be estimated from the available data.

In Table 4, adverse reactions are presented by frequency category based on spontaneous reporting rates, when known.

Table 4. Adverse Reactions Identified During Post-marketing Experience with Sibelium by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class (SOC)	Preferred Term (PT)	Frequency Category Estimated from Spontaneous Reporting Rates
Immune System Disorders	Hypersensitivity	Very rare
PsychiatricDisorders	Insomnia	*Very rare*
	Anxiety	*Very rare*
Nervous System Disorders		
	Akathisia	*Very rare*
	Bradykinesia	*Very rare*
	Cogwheel rigidity	*Very rare*
	Dyskinesia	*Very rare*
	Essential tremor	Very rare
	Extrapyramidal disorder	Very rare
	Parkinsonism	Very rare
	Gait disturbance	Very rare
	Sedation	Very rare
	Tremor	Very rare

Vascular Disorders	Hypotension	Very rare
	Flushing	Very rare
Gastrointestinal Disorders	Dyspepsia	Very rare
	Nausea	Very rare
	Vomiting	Very rare
Skin and Subcutaneous Tissue Disorders	Angioedema	Very rare
	Urticaria	Very rare
	Pruritus	Very rare
	Rash	Very rare
	Erythema	Very rare
Musculoskeletal and Connective Tissue Disorder	Muscle rigidity	Very rare
Reproductive System and Breast Disorders	Galactorrhea	*Very Rare*

Overdose

Symptoms and signs

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 were sedation, agitation and tachycardia.

Treatment

There is no specific antidote. Activated charcoal may be given if considered appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: antivertigo preparations. ATC code: N07CA03.

Flunarizine is a selective calcium antagonist. It prevents cellular calcium overload by reducing excessive transmembrane calcium influx. Flunarizine has no effect on contractility or conduction of the heart.

Pharmacokinetic Properties

Absorption

The drug is well absorbed reaching peak plasma concentrations within 2-4 hours and reaching steady-state at 5-6 weeks.

Flunarizine is well absorbed (>80%) from the gastrointestinal tract, reaching peak plasma concentrations within 2 to 4 hours after oral dosing. Under conditions of reduced gastric acidity (higher gastric pH), bioavailability may be moderately lower.
Plasma concentrations of flunarizine reach steady-state after approximately 8 weeks of once-daily multiple dosing and are about 3-fold higher than those observed after a single dose. Steady-state flunarizine concentrations are proportional over a dose range of 5 mg to 30 mg.

Distribution
Flunarizine is >99% bound to plasma proteins. It has a large volume of distribution of approximately 78 L/kg in healthy subjects and approximately 207 L/kg in epileptic patients indicating extensive distribution into extravascular tissue. The drug quickly crosses the blood brain barrier; concentrations in the brain are approximately 10 times higher than those in plasma.

Metabolism
Flunarizine is metabolized in the liver into at least 15 metabolites. The primary metabolic pathway is CYP2D6.
Elimination
Flunarizine is primarily eliminated as parent drug and metabolites through the feces via bile. Within 24 to 48 hours after administration, approximately 3% to 5% of the administered dose of flunarizine is eliminated in the feces as parent drug and metabolites and less <1% is excreted as unchanged drug in urine. Its terminal elimination half-life is highly variable, ranging from 5 to 15 hours in most individual subjects after a single dose. Some subjects show measurable plasma concentrations of flunarizine (>0.5 ng/mL) for a prolonged time period (up to 30 days), possibly due to redistribution of the drug from other tissues.

NON-CLINICAL INFORMATION
Preclinical effects of a CNS nature (e.g., sedation, salivation, ataxia) were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

PHARMACEUTICAL PARTICULARS
List of Excipients
The inactive ingredients are Colloidal Silicon Dioxide, Lactose, Magnesium Stearate, Purified Water, Starch, Croscarmellose Sodium, Hydroxypropylmethylcellulose, Polysorbate 20, Microcrystalline Cellulose.

Shelf Life
See Blister & Shelf unit for expiry date.

Special Precautions for Storage

Store at or below 30^0C, protected from light & moisture.

Keep out of the sight & reach of children.

Nature and Contents of Container

Available in 30 tablets blister pack.

Made in India by:

Johnson & Johnson Pvt. Ltd.,
Gala No. 3, BULDG No. B-2 Citylink Warehousing Complex,
S.No. 120-121, Mumbai Nashik Highway, Village Vadpe,
Taluka – Bhiwandi -421302, Maharashtra**.**

Manufactured at:

Encore Healthcare Pvt. Ltd.,
Plot No. D-5, M.I.D.C, Industrial Area,
Paithan, Aurangabad – 431148.

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