PRODUCT NAME

SIBELIUM® (flunarizine hydrochloride).

DOSAGE FORMS AND STRENGTHS

Tablets.

5 mg tablets: White, oblong tablet with the inscription "J-C" on one side and "FL5" on the other side. Each tablet contains flunarizine hydrochloride equivalent to 5 mg flunarizine base.

10 mg tablets: White, circular flat, bevel-edged, half-scored tablet with the inscription "JANSSEN" on one side and "F1/10" on the other side. Each tablet contains flunarizine hydrochloride equivalent to 10 mg flunarizine base.

For excipients, see 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 aged 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 1 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 post-natal 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 hydrochloride based on the comprehensive assessment of the available adverse event information. A causal relationship with flunarizine hydrochloride 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

Postmarketing data

Adverse events first identified as adverse reactions during postmarketing experience with SIBELIUM® are included in Table 4. In this table, adverse reactions are presented by frequency category based on spontaneous reporting rates, with frequencies 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

Table 4. Adverse Reactions Identified During Postmarketing Experience with SIBELIUM® by Frequency Category Estimated From Spontaneous Reporting Rates

Immune System Disorders		
	Hypersensitivity	*Very rare*
Psychiatric Disorders		
	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.

Pharmacodynamic effects

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 INFORMATION

List of Excipients

The inactive ingredients are: colloidal anhydrous silica, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polysorbate.

Incompatibilities

Not applicable.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Do not store above 25° C. Protect from light.
Keep out of reach of children.

Nature and Contents of Container

Blisters: Polyvinylchloride foil, aluminum foil.

Instructions for Use and Handling

Not applicable.

Instructions for Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT
27 May 2016