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SIBELIUM® Capsules

Janssen

NAME OF THE MEDICINAL PRODUCT

Trade name
SIBELIUM®
International Non-Proprietary Name (Modified) (rINNM) flunarizine hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SIBELIUM® capsule contains flunarizine hydrochloride equivalent to 5 mg flunarizine base.

For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Capsules
5 mg capsules
White powder filled in capsules (size 4) made up of red cap and dark grey body.

CLINICAL PARTICULARS

Therapeutic 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.

Posology and Method of Administration

(See also Special Warnings and Special Precautions for Use).

• Migraine prophylaxis

- Starting dose:

Treatment is started at 10 mg daily (at night) for patients younger than 65 years of age and at 5 mg daily for patients older than 65 years. If, during this treatment, depressive, extrapyramidal or other unacceptable adverse experiences occur, administration should be discontinued. If, after 2 months of this initial treatment, no significant improvement is observed, the patient should be considered a non-responder and administration should also be discontinued.

- Maintenance treatment:

If the patient responds satisfactorily and if a maintenance treatment is needed, the dose should be decreased so that each week he/she has 5 days 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 two months. If, however, no significant improvement is observed after one month for chronic vertigo or after two months for paroxysmal vertigo, the patient should be considered a non-responder and administration should be discontinued.

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 Special Warnings and Special Precautions for Use and Undesirable Effects).

Special Warnings and Special Precautions for Use

This treatment 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 (for duration of treatment see also Posology and Method of Administration).

Interaction with Other Medicinal Products and Other Forms of Interaction

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

Sibelium is not contra-indicated 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 Lactation

Use during 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.

Use during lactation

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. Nursing should therefore be discouraged in women taking Sibelium.

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.

Undesirable Effects

Clinical Trial Data

Placebo-Controlled Double-Blind Data – Adverse Drug 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 Drug Reactions (ADRs) reported by ≥1% of Sibelium treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug 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 Breast pain	2.8 1.2	1.2 0.4
Investigations		
Weight increased	11.3	2.8

Active Comparator-Controlled Data – Adverse Drug Reactions Reported at ≥1% Incidence

Two double-blind active comparator-controlled trials were selected to determine the incidence of ADRs.

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.

ADRs 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 Drug 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	
Stomach discomfort	2.3
General Disorders and Administration Site Conditions	
Fatigue	2.9

Placebo- and Active Comparator-Controlled Data – Adverse Drug Reactions Reported at <1% Incidence

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

Table 3. Adverse Drug 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
Generalised Oedema
Asthenia
Oedema Peripheral

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with Sibelium are included in Table 4. In this 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

In Table 4, ADRs are presented by frequency category based on spontaneous reporting rates

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

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*
Sedation	*Very rare*
Tremor	*Very rare*
Gastrointestinal Disorders	
Nausea	*Very rare*
Musculoskeletal and Connective Tissue Disorder	
Muscle rigidity	*Very rare*
Skin and Subcutaneous Tissue Disorders	
Erythema	*Very rare*
Reproductive System and Breast Disorders	
Galactorrhea	*Very Rare*

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 were sedation, agitation and 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.

PHARMACOLOGICAL PROPERTIES

ATC Code, N2C: Anti-Migraine Preps

Pharmacodynamic Properties

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

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

Absorption

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.

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.

Multiple-Dose

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.

Preclinical Safety Data

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 of the capsules are lactose monohydrate, maize starch, talc, magnesium stearate and colloidal anhydrous silica.

The capsule shell contains erythrosine, yellow ferric oxide, titanium dioxide, black ferrous oxide, red ferric oxide, and gelatin.

Incompatibilities

Not applicable.

Shelf Life

Observe expiry date on the outer pack.

Special precautions for storage

Store between 15°C and 30°C.

Keep out of reach of children.

Nature and Contents of Container
Blisters: Polyvinylchloride foil, PVC/LDPE/PDVC, aluminum foil.

Instructions for Use and Handling and Disposal
Not applicable

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