PACKAGE INSERT

SCHEDULING STATUS

Schedule 2

1. NAME OF THE MEDICINE

SIBELIUM® T 5 mg tablet

SIBELIUM® 10 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SIBELIUM T 5 mg tablet contains flunarizine hydrochloride equivalent to 5 mg flunarizine.

Each tablet also contains 57,42 mg lactose monohydrate.

Each SIBELIUM 10 mg tablet contains flunarizine hydrochloride equivalent to 10 mg flunarizine. Each tablet also contains 51,53 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SIBELIUM T 5 mg tablet: White, oblong tablet with the inscription “J-C” on one side and “FL 5” on the other side.

SIBELIUM 10 mg tablet: White, circular, flat, bevel-edged, half-scored tablet with the inscription “JANSSEN” on one side and “FI /10” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

SIBELIUM is indicated in:

- 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).

4.2 Posology and method of administration

Adults and elderly (18 years of age and older)

- ***Migraine prophylaxis***

Starting dose:

Treatment is started at two 5 mg tablets (10 mg) SIBELIUM at night in 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. 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 a patient is responding 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 medicine free days

Even if the prophylactic maintenance treatment is successful and well tolerated, it should be interrupted after 6 months and it should be 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 1 month of treatment for chronic

vertigo or after 2 months treatment for paroxysmal vertigo, the patient should be considered a non-responder and administration should be discontinued**.**

The dose will be as described below:

- Take the same number of tablets you are used to taking (1 or half a tablet(s) every day before going to bed for 5 days in a row; and do not take any tablets for 2 days in a row.

  Repeat this pattern (5 days with medicine followed by 2 days with no medicine) for the rest of the treatment.

Special populations

Paediatrics (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 sections 4.4 and 4.8). 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.

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

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

Paediatrics (17 years of age and younger) – vertigo

The safety and efficacy of SIBELIUM for treatment of vertigo in paediatric patients have not been established.

4.3 Contraindications:

Hypersensitivity to flunarizine or any other ingredient in the formulation. 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 sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

SIBELIUM is not suited for aborting a migraine attack. The possible occurrence of an attack is therefore no reason to increase the dose of SIBELIUM.

This treatment may give rise to extrapyramidal and depressive symptoms and reveal Parkinsonism, especially in predisposed patients such as the elderly. SIBELIUM should therefore be used with caution in such patients.

SIBELIUM should be used with care in patients with depression or those being prescribed other agents, such as phenothiazines, concurrently, which may cause extrapyramidal side effects.

Fatigue may increase progressively during SIBELIUM therapy; in this event 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 section 4.2).

Patients who are intolerant to lactose should not take SIBELIUM, as the tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take SIBELIUM.

4.5 Interaction with other medicines and other forms of interaction:

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

Galactorrhoea has been reported in some women on oral contraceptives within the first two months of SIBELIUM treatment.

Hepatic enzyme inducers such as carbamazepine and phenytoin may interact with flunarizine by increasing its metabolism. An increase in dosage of SIBELIUM may be required.

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.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy has not been established.

Breastfeeding women should not take SIBELIUM.

4.7 Effects on ability to drive or operate machinery

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

4.8 Undesirable effects

Clinical trial data

The safety of SIBELIUM (5 to 10 mg/day) was evaluated in 247 flunarizine-treated subjects who participated in two placebo-controlled clinical trials in the treatment of vertigo and migraine, and in 476 flunarizine-treated subjects who participated in two comparator-controlled clinical trials in the treatment of vertigo and/or migraine. Based on pooled safety data from these clinical trials, the most commonly reported (≥ 4 % incidence) adverse reactions were: Increased weight (11 %), somnolence (9 %), depression (5 %), increased appetite (4 %); and rhinitis (4%).

Including the above-mentioned adverse reactions, the following table displays adverse reactions that have been reported with the use of SIBELIUM from clinical trials. The displayed frequency categories use the following convention:

Very common (≥1/10); common (≥1/100 to 1/10) and uncommon (≥1/1 000 to <1/100).

System Organ Class	**Adverse reactions**
	Frequency categories

	Very common (≥1/10)	**Common (≥1/100 to 1/10)**	**Uncommon (≥1/1 000 to < 1/100)**
Infections and infestations		Rhinitis	
Metabolism and nutrition disorders		Increased appetite	
Psychiatric disorders		Depression	Depressive symptom Sleep disorder Apathy
Nervous system disorders		Somnolence	Abnormal coordination Disorientation Lethargy Paraesthesia Restlessness Sluggishness Tinnitus Torticollis
Cardiac disorders			Palpitations
Gastrointestinal disorders		Constipation Upper abdominal pain	Intestinal obstruction Dry mouth Gastrointestinal disorder

Skin and subcutaneous tissue disorder			Hyperhidrosis
Musculoskeletal and connective tissue disorders		Myalgia	Muscle spasms Muscle twitching
Reproductive system and breast disorders		Irregular menstruation Breast pain	Menorrhagia Menstrual disorder Oligomenorrhoea Breast hypertrophy Decreased libido
General disorders and administration site conditions		Fatigue	Generalised oedema Peripheral oedema Asthenia
Investigations	Increased weight		

Post-marketing Data

Adverse events first identified during post-marketing experience with SIBELIUM are included in in the table below.

Adverse Reactions Identified During Post-marketing Experience with SIBELIUM	
Immune System Disorders	Hypersensitivity
Psychiatric Disorders	Insomnia Anxiety

Nervous System Disorders	Akathisia Bradykinesia Cogwheel rigidity Dyskinesia Essential tremor Extrapyramidal disorder Parkinsonism Gait disturbance Sedation Tremor
Vascular Disorders	Hypotension Flushing
Gastrointestinal Disorders	Dyspepsia Nausea Vomiting
Skin and Subcutaneous Tissue Disorders	Angioedema Urticaria Pruritus Rash Erythema
Musculoskeletal and Connective Tissue Disorder	Muscle rigidity
Reproductive System and Breast Disorders	Galactorrhoea

Paediatric population

The frequency, type and severity of adverse reactions are expected to be similar in children and adults.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

4.9 Overdose:

Symptoms

Sedation and asthenia may be expected to occur. Acute overdosage has been reported and the observed symptoms were sedation, agitation and tachycardia.

Treatment

Treatment of acute overdosage consists of charcoal administration, and supportive measures. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A.5.7.1 Antihistaminic, anti-emetics and antivertigo preparations - Antihistamines.

Mechanism of action:

Flunarizine is a selective calcium antagonist. It prevents cellular calcium overload by reducing excessive transmembrane calcium influxes.

5.2 Pharmacokinetic properties

Absorption:

Flunarizine is well absorbed, reaching peak plasma levels 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 extra vascular tissue. Flunarizine quickly crosses the blood brain barrier; concentrations in the brain are approximately 10 times higher than those in plasma.

Biotransformation:

Flunarizine is metabolised 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 faeces via bile. Within 24 to 48 hours after administration, approximately 3 % to 5 % of the administered dose of flunarizine is eliminated in the faeces as parent compound and

metabolites and less < 1 % is excreted as unchanged compound 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 compound from other tissues.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Colloidal anhydrous silica, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polysorbate 20.

6.2 Incompatibilities:

Not Applicable.

6.3 Shelf life:

SIBELIUM® 10 mg tablet - 36 Months

SIBELIUM® T 5 mg tablet - 24 Months

6.4 Special precautions for storage:

Store at or below 25 °C.

Protect from light and store in a dry place.

Blisters must be kept in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container:

SIBELIUM T 5 mg tablet: Printed carton containing one or more aluminium/aluminium strips of 10 tablets.

SIBELIUM 10 mg tablet: Carton containing one or more blister strips of 7 or 10 tablets each.

7. HOLDER OF CERTIFICATE OF REGISTRATION



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8. REGISTRATION NUMBER(S)

SIBELIUM® T 5 mg tablet: 43/5.7.1/0451

SIBELIUM® 10 mg tablet: M/5.7.1/530

9. DATE OF FIRST AUTHORISATION

SIBELIUM® T 5 mg tablet: 26 October 2012

SIBELIUM® 10 mg tablet: 15 July 1981

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA:

12 May 2022