

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0748/031/001

Case No: 2057802

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Janssen-Cilag Ltd

50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sibelium 5mg Hard Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/04/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sibelium 5mg Hard Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of flunarizine as flunarizine dihydrochloride.

Excipients – Contains Lactose Monohydrate 122.7mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Opaque, hard, gelatin capsules with a dark grey body and a red cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the prophylaxis of migraine. The limited information available for periods longer than 12 months has shown flunarizine to continue to be effective. Patients should be regularly reviewed to assess their response to treatment, and if a sustained attack-free period is established, interrupted flunarizine treatment should be considered.

4.2 Posology and method of administration

Adults only:

Starting Dose

Treatment is started at 10 mg daily (at night) in patients less than 65 years of age and at 5mg daily (at night) in patients over 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 be discontinued.

Maintenance Treatment

If the patient is responding satisfactorily and a maintenance treatment is needed, the same daily dose should be used, but this time interrupted by two successive drug-free days every week, e.g. Saturday and Sunday.

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.

Elderly: As above.

Children, Infants and Neonates: Not recommended.

4.3 Contraindications

Use in patients suffering from current depressive illness or with a history of recurrent depression.

Use in patients with diseases of the extrapyramidal nervous system such as Parkinson's Disease, or a history of such.

4.4 Special warnings and precautions for use

This product may give rise to fatigue, which in rare cases may increase progressively. In this event, the therapy should be discontinued and possibly initiated again at a lower dosage.

Accumulation may occur if given at dose levels higher than recommended, with an increased incidence of side effects.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Female patients with a history of depressive illness may be at particular risk of depression during chronic treatment with this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

When used in conjunction with anti-hypertensive drugs, dosage of the latter may need adjustment.

Galactorrhoea has been reported in some female patients on oral contraceptives within the first two months of flunarizine treatment.

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

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 of 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 Pregnancy and lactation

The product should not be used during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

Flunarizine may cause drowsiness, and patients receiving it should not drive or operate machinery unless it has been shown that their physical and mental capacity remain unaffected.

4.8 Undesirable effects

The safety of Sibelium was evaluated in 247 flunarazine-treated subjects who participated in two placebo-controlled clinical trials in the treatment of vertigo and migraine, respectively, and in 476 flunarazine-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 ($\geq 4\%$ incidence) Adverse Drug Reactions (ADRs) were: Weight Increased (11%), Somnolence (9%), Depression (5%), Increased Appetite (4%); and Rhinitis (4%).

Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of Sibelium from either clinical-trial or post-marketing experiences. The displayed frequency categories use the following convention:

Very common (≥1/10); common (≥1/100 to 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available date).

System Organ Class	Adverse Drug reactions			
	Frequency Category			
	Very common (≥ 1/10)	Common (≥1/100 to 1/10)	Uncommon (≥ 1/1,00 to <1/100)	Not Known
Infections and Infectations		Rhinitis		
Metabolism and Nutrition disorders		Increased appetite		
Psychiatric Disorders		Depression Insomnia	Depressive Symptoms; Sleep Disorder; Apathy; Anxiety	
Nervous System Disorders		Somnolence	Coordination Abnormal; Disorientation; Lethargy; Paraesthesia Restlessness; Sluggishness; Tinnitus; Torticollis	Akathisia; Bradykinesia; Cogwheel; Rigidity; Dyskinesia; Essential Tremor; Extrapyrāmida 1 Disorders; Parkinsonism; Sedation; Tremor
Cardiac Disorders			Palpitations	
Gastrointestinal Disorders		Constipation; Stomach Discomfort; Nausea	Intestinal Obstruction; Dry mouth; Gastrointestinal Disorders;	
Skin and Subcutaneous tissue disorder			Hyperhidrosis;	Erythema;
Musculoskeletal and Connective Tissue Disorders		Myalgia;	Muscle Spasms; Muscle Twitching;	Muscle Rigidity;
Reproductive System and Breast Disorders		Menstruation Irregular; Breast Pain;	Menorrhagia; Menstrual Disorder; Oligomenorrhoea; hypertrophy Breast; Libido Decreased	Galactorrhoea
General Disorders and Administration Site Conditions		Fatigue	Generalised Oedema; Oedema Peripheral; Asthenia;	
Investigations	Weight Increased;			

4.9 Overdose

On the basis of the pharmacological properties of the drug, sedation and asthenia may be expected to occur. A few cases of acute overdosage have been reported and the observed symptoms were sedation, agitation and tachycardia. Treatment of acute overdosage consists of charcoal administration, induction of emesis or gastric lavage and supportive measures. No specific antidote is known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code, N2C: Anti-Migraine Preps

Class IV selective calcium entry blocker, which reduces arterial and arteriolar smooth muscle spasm.

5.2 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 or approximately 78L/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 single dose. Steady-state flunarizine concentrations are proportional over a dose range of 5 mg to 30 mg.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Content

Lactose monohydrate
Maize starch
Talc
Magnesium stearate
Colloidal anhydrous silica

Capsule Shell

Yellow iron oxide (E172)
Red iron oxide (E172)
Black iron oxide (E172)
Erythrosine sodium (E127)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The capsules are supplied in PVC/Aluminium blister packs in a carton containing 20 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag Ltd
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0748/031/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 November 1982

Date of last renewal: 26 April 2009

10 DATE OF REVISION OF THE TEXT

May 2009