Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sibelium 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of flunarizine as flunarizine dihydrochloride.

Excipients with known effect:
Each tablet also contains 57.42mg lactose monohydrate.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, oblong tablet inscribed 'J-C' on one side and 'FL 5' on the other side.

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 and elderly (18 years of age and older):

Starting Dose

Treatment is started at 10 mg daily (at night) for adult patients aged 18 to 64 years and at 5 mg daily (at night) 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 Sections 4.4 and 4.8). 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, eg 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.

Children, Infants and Neonates: Not recommended.

4.3 Contraindications

Use in patients with current depressive illness or with a history of recurrent depression (see Sections 4.4 and 4.8).

Use in patients with pre-existing symptoms of Parkinson's Disease or other extrapyramidal disorders (see Sections 4.4 and 4.8).

Sibelium Tablets are contra-indicated in patients with a known hypersensitivity to flunarizine, or to any excipients contained in the formulation.

4.4 Special warnings and precautions for use

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

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.

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

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

In rare cases fatigue may increase progressively during flunarizine therapy. In this event, the therapy should be discontinued and possibly initiated again at a lower dosage.

Lactose
Flunarizine tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Each tablet contains less than 1 mmol sodium (23 mg), and is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interactions

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. After repeated dosing in migraine patients, systemic exposure to flunarizine increased by 14%. When flunarizine was co-administered with topiramate 50 mg every 12 hours, repeated dosing resulted in a 16% increase in systemic exposure to flunarizine. 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

4.6.1 Use during pregnancy
There are no data from the use of flunarizine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development.
As a precautionary measure, it is preferable to avoid the use of flunarizine during pregnancy.

4.6.2 Use during lactation
It is unknown whether flunarizine is excreted in human milk. Animal studies have shown excretion of flunarizine in breast milk. A decision on whether to discontinue breast-feeding or to continue/discontinue therapy with flunarizine should be made taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

4.7 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.

4.8 Undesirable effects

The safety of Sibelium (5 to 10mg/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: Weight Increased (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 both clinical trial and post-marketing experiences. The displayed frequency categories use the following convention:

Very common (≥1/10); common (≥1/100 to 1/10); uncommon (≥1/1,00 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Adverse Reactions			
	Frequency Category			
	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not known
Immune System Disorders			Hypersensitivity	
Infections and Infestations		Rhinitis;		
Metabolism and Nutrition disorders		Increased Appetite		
Psychiatric Disorders		Depression; Insomnia	Depressive Symptom; Sleep Disorder; Apathy; Anxiety;	
Nervous System Disorders		Somnolence	Coordination Abnormal; Disorientation; Lethargy; Paraesthesia; Restlessness; Sluggishness: Tinnitus; Torticollis	Akathisia; Bradykinesia; Cogwheel Rigidity; Dyskinesia; Essential Tremor; Extrapyramidal Disorder; Parkinsonism; Gait disturbance; Sedation; Tremor
Cardiac Disorders			Palpitations	
Vascular Disorders			Hypotension; Flushing	
Gastrointestinal Disorders		Constipation; Abdominal pain upper; Nausea	Intestinal Obstruction; Dry Mouth; Gastrointestinal Disorder; Dyspepsia; Vomiting	
Hepatobiliary disorders				Hepatic transaminases increased

Skin and Subcutaneous tissue disorder			Hyperhidrosis; Urticaria; Rash	Erythema; Angioedema; Pruritis
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			

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms and signs
On the basis of the pharmacological properties of the drug, sedation and asthenia may be expected to occur. Cases of acute overdosage (up to 600 mg in one intake) have been reported and the observed symptoms were sedation, agitation and tachycardia.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-vertigo Preparations, ATC Code: N07CA03

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 of approximately 78 L/kg in healthy subjects and approximately 207 L/kg in epileptic patientsindicating 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 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 drug and metabolites and <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.

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.

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

Lactose monohydrate
Maize starch
Magnesium stearate
Colloidal anhydrous silica
Hypromellose
Polysorbate 20
Microcrystalline cellulose
Croscarmellose sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

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

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 Sciences Ireland UC
Barnahely
Ringaskiddy
Cork
P43 FA46
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22612/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th January 2009

Date of last renewal: 29th January 2014

10 DATE OF REVISION OF THE TEXT

August 2020