This module reflects the assessment of a national type II variation for Sibelium 10 mg tablets. The addition of dose instructions for paediatric patients in the migraine prophylaxis indication was proposed. The procedure was finalised on 23 December 2015. The proposed changes were not approved.

A list of literature references is given on page 17.
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<th>Abbreviation</th>
<th>Full Form</th>
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<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AC</td>
<td>Active Controlled</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>EPS</td>
<td>Extrapyramidal Symptoms</td>
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<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone (FSH)</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board of the Netherlands</td>
</tr>
<tr>
<td>NVN</td>
<td>Nederlandse Vereniging voor Neurologie</td>
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<td>PD</td>
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<td>TSH</td>
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</tr>
</tbody>
</table>
I. RECOMMENDATION

A national type II variation was submitted for Sibelium 10 mg tablets (flunarizine) in order to add dose instructions for paediatric patients aged 6-17 to section 4.2 of the SmPC, for the indication prophylaxis of migraine. Based on the review of the submitted data, the Medicines Evaluation Board of the Netherlands (MEB) considers that the indication needs to be restricted to adult patients. No dose recommendation can be given for children and adolescents because there are doubts about safety in this age group.

II. EXECUTIVE SUMMARY

II.1 Introduction

Sibelium 10 mg has been registered in the Netherlands by Janssen-Cilag B.V. since 18 April 1984. Flunarizine is a selective calcium channel blocker. It prevents cellular calcium overload by reducing excessive transmembrane calcium influx.

The approved indications are:

- Prophylaxis of migraine in patients with frequent, severe attacks insufficiently responding to other treatment options, or in whom another therapy caused unacceptable side effects.
- Symptomatic treatment of vestibular vertigo due to a diagnosed functional disorder of the vestibular system.

II.2 Scope of the variation

The current SmPC provides no lower age limit for patients receiving flunarizine treatment and there is no specific dosage recommendation for children and adolescents. The MAH requested to add dose instructions for paediatric patients aged 6-17 to section 4.2 of the SmPC, for the indication prophylaxis of migraine. The MAH submitted a review of the available clinical trial data regarding the use of flunarizine in children and adolescents for the prevention of migraine. Evidence from several published studies is referred to, including pharmacodynamic studies, 2 placebo controlled studies (pivotal studies), and additionally active controlled and uncontrolled studies (supportive studies).

III. CLINICAL ASPECTS

III.1 Introduction

Diagnostics

According to the International Headache Society, migraine is defined as headache attacks lasting 4-72 hours which fulfill at least 2 of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs). During headache, at least one of the following should be present: nausea and/or vomiting, photophobia and phonophobia.

Epidemiology

The prevalence of migraine headache in children and adolescents is estimated at 7%-10% (Abu-Arafeh et al, 2010, Wöber-Bingöl, 2013, Özge et al. 2013, Fendrich et al., 2007). Most cases are episodic migraine and only a minority of the cases is chronic. The study of Özge et al.(2013) which distinguished episodic from chronic migraine showed a total prevalence of 10.4% of which only 1.7% was chronic and the remaining 8.6% was episodic. Prevalence of migraine headache is higher in girls compared to boys and in adolescents compared to children.
Alternative treatments
Currently there are several medicinal products registered for migraine prophylaxis in adults: Sibelium (flunarizine), Deseril (methysergide), Selokeen (metoprolol), Sandomigran (pizotifen), propranolol, and Topamax (topiramate; as 2nd line). Only pizotifen and propranolol are indicated for paediatric patients: there is a dose instruction in SmPC section 4.2 for children >2 for pizotifen and dose instructions for children older and younger than 12 for propranolol. Imigran (Sumatriptan nasal spray) is registered for the acute treatment of migraine attacks in adolescents (12-17 years old).

Treatment guideline
The Dutch Society for Neurology (Nederlandse Vereniging voor Neurologie (NVN)) treatment guideline for headache dating 2007 indicates that:

“There are no methodologically adequate clinical trials in children with migraine prophylactics. Drug prophylaxis is recommended only in the case of severe attacks or attacks lasting for a long period (more than 3 months) or that are frequent (more than 2 attacks per month). Treatment should be administered for not more than 6 months, thereafter one can attempt to taper off.”

Although the Dutch treatment guideline does mention flunarizine as a treatment option for migraine in children and adolescents, it is recommended only as second choice “given the severe extrapyramidal side effects”.

CHMP guideline
The EMA guideline on clinical investigation of medicinal products for the treatment of migraine (London, 24 January 2007 Doc. Ref. CPMP/EWP/788/01 Rev. 1) indicates that patients who are not satisfactorily managed with acute treatment may receive prophylactic treatment, which is usually started at an attack rate of 2 or more per month. Separate studies in children (6 - < 12 years age) and adolescents (12-18 years of age) should be conducted for acute and prophylactic treatment.

In order to determine the characteristics and the frequency of attacks per month, the guideline recommends that patients included in prophylaxis trials have a 3-month well-documented retrospective history. In addition, the trial should include a prospective baseline (run-in period) of at least one month. Randomisation should occur after this run-in period. Treatment periods should be at least 3 months. The guideline further recommends that patients be followed for at least 4 weeks after termination of the treatment period to detect possible rebound phenomena.

The EMA guideline recommends that primary endpoint is the frequency of attacks within a pre-specified period, e.g. the mean frequency of attacks per 4 weeks or during the final 4 weeks of a 3-month study duration. Assessment of pain should be based on scales validated for migraine in paediatric patients. Prophylaxis studies should be randomised, placebo controlled and preferably active controlled with a cross-over or parallel group design. In addition, especially for prophylactic treatment, long-term safety data are required for the paediatric population. Specifically, this includes evidence regarding the impact of treatment on growth and endocrine development. In addition, if in the randomised controlled trials the safety profile indicates an effect on cognitive function (e.g., sedation, attention), long-term safety data on cognitive function may be needed.

Submitted clinical documentation
The MAH presented an overview of published studies with flunarizine, including:

- 4 open label pharmacodynamic studies
- 1 pharmacokinetic study
- 2 placebo controlled studies
- 4 active comparative studies
- 2 uncontrolled trials
- 4 retrospective studies

1 Richtlijnen diagnostiek en behandeling Chronisch recidiverende hoofdpijn Zonder neurologische afwijkingen; 1ste herziening, 2007.
III.2 Pharmacokinetics

The MAH proposed a dose recommendation for children and adolescents of 5 mg/day which can eventually be increased to 10 mg/day. Pharmacokinetic data of flunarizine in paediatric patients were found in 2 articles. In the first (Cortelli et al., 1988), 1 month treatment with daily doses of 5 mg in paediatric patients of 10 to 16 years of age led to mean ± SD serum levels of 19.3 ± 9.4 ng/mL. In the second, conducted in paediatric patients with epilepsy (Hoppu et al., 1995), a mean end dose of 0.17 mg/kg/day (range: 0.05 - 0.35 mg/kg/day) flunarizine over a mean duration of 10.1 months led to a mean plasma flunarizine concentration of 29 ng/mL (range: 11 - 53 ng/mL). In this second study, other parameters were also studied: mean $C_{\text{max}}$ was 65.0 ng/mL (range: 33 - 108 ng/mL), mean $t_{\text{max}}$ was 2.7 hours (range: 1 - 8 hours), and mean t1/2 was 23.2 days (range: 7 - 48 days).

From a pharmacokinetic point of view, the provided data for the paediatric population is too limited to determine the appropriate dose for this age group. In the 2 studies provided, 2 different doses were used: 5 mg/day given for one month (Cortelli et al., 1988) and 0.1-0.3 mg/kg/day for about 10 months (Hoppu et al., 1995). The latter study is more relevant as steady-state levels were achieved. However, flunarizine was an add-on treatment with other antiepileptic drugs (i.e. carbamazepine, valproate, clonazepam, phenytoin and ethosuximide). The flunarizine levels could have been influenced by the concomitant antiepileptic drugs, as according to the literature, carbamazepine and phenytoin may decrease the serum concentration of flunarizine. This is stated in section 4.5 of the SmPC. Hence, comparison of these data with adult data is difficult.
### III.3 Pharmacodynamics

The four pharmacodynamic studies are summarized in the table below.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Product / indication</th>
<th>Dosage</th>
<th>Comparator</th>
<th>Report type / treatment duration</th>
<th>No. of patients fluanizine / total (age range)</th>
<th>Efficacy results / pharmacokinetics</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. Cortelli 1985</td>
<td>Fluanizine / migraine</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>None</td>
<td>Open-label, uncontrolled study / 30 days</td>
<td>5/5 (11 - 16 years) 3 m 2 f</td>
<td>No results on efficacy provided. Serum concentrations of fluanizine obtained after 30 days of therapy were 21.1 ± 13.4 mg/mL (range: 5.1 - 35.3 mg/mL).</td>
<td>No notable AEs mentioned. All patients completed the treatment.</td>
</tr>
<tr>
<td>P. Cortelli 1988</td>
<td>Fluanizine / migraine</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>None</td>
<td>Open-label, uncontrolled study / 30 days</td>
<td>17/17 (10 - 16 years) 11 m 6 f</td>
<td>No results on efficacy provided. At the end of treatment, mean ± SD fluanizine serum concentration was 19.3 ± 9.4 mg/mL (range: 5.1 - 30 mg/mL).</td>
<td>4 patients reported slight drowsiness. All patients completed the treatment.</td>
</tr>
<tr>
<td>V. Guidetti 1987</td>
<td>Fluanizine / migraine</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>None</td>
<td>Open-label, uncontrolled study / 2 months</td>
<td>13/13 (10 - 13 years) 9 m 4 f</td>
<td>Efficacy in reducing the frequency of migraine attacks in all patients.</td>
<td>No notable adverse effects could be observed. One patient dropped-out (no reason mentioned). No statistically significant change in hormonal levels could be observed after treatment with fluanizine.</td>
</tr>
<tr>
<td>T. Hufnagel 2009</td>
<td>Fluanizine / migraine</td>
<td>5 - 10 mg/day No mg/kg/day provided</td>
<td>Cyproheptadine / amitriptyline / propranolol</td>
<td>Open-label, comparator-controlled study / 4 months</td>
<td>19/77 Mean ± SD age: 10.2 ± 2.7 years 33 m 44 f</td>
<td>Amitriptyline was most effective in reducing headache frequency (80.1% improvement), followed by propranolol (78.3%) and fluanizine (71.5%). Cyproheptadine proved to be the most effective drug in its capacity to reduce duration (62.2% improvement). Amitriptyline was better than fluanizine in reducing the duration (33% improvement vs 16.3%). Cyproheptadine was most effective in alleviating headache severity (61.5% improvement), followed by propranolol (54.3%).</td>
<td>No notable AEs were reported. All patients completed the treatment.</td>
</tr>
</tbody>
</table>
All 4 studies were small, open label studies, in which the included children and adolescents were treated with flunarizine. Patients received 5 mg flunarizine, except in the study by Hirfanoglu et al. (2009) where 19 patients received 5-10 mg.

Results of the study by Hirfanoglu et al. (2009) suggest that flunarizine is less effective compared to cyproheptadine, propranolol, and amitriptyline. Only propranolol has the indication migraine prophylaxis in children. The study report does not provide details on randomization and hence the value of the results is unclear.

Results showed that basal secretion of growth hormone was significantly reduced (1.25 ± 0.25 vs. 0.75 ± 0.25 ng/ml; p < 0.01) after treatment in one study (Cortelli et al., 1985) but showed no change after treatment in the other 2 studies which measured growth hormone (Cortelli et al., 1988; Guidetti et al., 1987).

The values of growth hormone before and after treatment with flunarizine are within normal range (= up to 20 ng/ml). However, the size of the change is d=0.50/0.25=2.0 and hence a very large effect size. The clinical relevance of this effect is not clear, but it may be a signal for safety problems associated with reduced growth hormone.

Peak concentration and area of prolactin were significantly higher after treatment (34 ± 9.8 vs. 40 ± 9.8 ng/ml; p < 0.01 for concentration and 68 ± 20 vs. 85 ± 20; p < 0.0025 for area) in the study by Cortelli et al (1985 and 1988). Other hormonal measurements (TSH, FSH) did not show any significant difference after flunarizine treatment.

The values of prolactin levels are largely outside normal range (2-17) before and after treatment. Effect size is d=0.6 (moderate).

Although no difference was observed in glucose tolerance tests after treatment, the percentages of HbA1c (7.04 ± 0.6 vs. 7.98 ± 1.0 p < 0.05) and HbA1c (4.76 ± 0.34 vs. 5.25 ± 0.52 p < 0.05) were significantly higher. Gonadic and adrenal functions did not significantly change after treatment with flunarizine.

The study by Hirfanoglu (2009) assessed the cytokines (tumor necrosis factor α [TNFa], interleukin-1β [IL1β], and interleukin-6 [IL6]) and leptin levels after treatment with cyproheptadine, amitriptyline, propranolol, or flunarizine. Results showed that all 3 cytokines levels decreased while leptin levels increased after treatment compared to before treatment. No correlation was found between cytokines levels and frequency, severity, duration of migraine attacks.

Discussion
The MAH argues that the results of the studies by Cortelli et al (1985 and 1988) are flawed as the levels of prolactin were pooled for male and female patients, while prolactin is known to be higher in women than in men. In addition, it is argued that all patients were tested before treatment and 1 month later, meaning that female patients could be in a different phase of menstrual cycle at the two measurements, leading to a change of prolactin levels. Furthermore, no evidence is provided as to whether tests were done at the same time of the day before and after treatment and since prolactin levels show circadian fluctuation, this alone could explain the difference observed.

Moreover, another study (Guidetti et al., 1987) concluded that flunarizine treatment did not have any effect on the hypothalamo-hypophyseal, beta pancreatic, gonadic, or adrenal function. However, the methodology used in this latter study was incompletely described and techniques may have influenced the results.
The MAH concludes that the 2 studies appear contradictory but both are inadequate studies or inadequately reported studies making it impossible to draw any definitive conclusions. In addition, the MAH argues that the clinical significance of the changes in cytokine levels in the study of Hirfanoglu et al (2009) is not clear as there was no correlation with outcomes (migraine frequency).

**Pharmacodynamic conclusion**

Prolactin increase was noted in 2 studies (Cortelli et al., 1985 and Cortelli et al., 1988). The argumentation of the MAH for the dismissal of the prolactin results is not acceptable. It is considered that the flaws identified in the studies (i.e. the inclusion of boys and girls, not taking into account phases on menstrual cycle), would serve to mask an effect on prolactin level rather than to bring it about. The pre-post within subjects comparisons are not expected to be influenced by gender differences. Moreover, the fact that measures were performed 1 month apart is likely to result in measures during the same phase of the female hormonal cycle. Therefore these results, with respect to increased prolactin, suggest that when examining safety in the clinical studies, special attention should be paid to adverse effects that are known to be associated with increased prolactin levels.

With respect to results concerning decreases in basal secretion of growth hormone, despite inconsistent results, given the prolactin findings, these results call for special attention in examining the safety of flunarizine in the areas of growth abnormalities, sexual maturation and weight.

The finding in one study of increased leptin levels after treatment suggests that flunarizine may cause changes in appetite. Therefore in clinical studies special attention should be paid to weight change and weight abnormalities.

Finally, the finding in one study of decreased cytokine levels after treatment suggests flunarizine may cause immune response abnormalities and therefore special attention should be paid to (opportunistic) infections related to the use of flunarizine.
### III.4 Clinical efficacy and safety

The two pivotal studies are summarized in the table below:

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Product/indication</th>
<th>Dosage</th>
<th>Comparator</th>
<th>Report type/treatment duration</th>
<th>No. of patients</th>
<th>Efficacy results</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. Sorge 1985</td>
<td>Flunarizine/migraine</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>Placebo</td>
<td>Double-blind, placebo-controlled study/3 months</td>
<td>24/48</td>
<td>Mean ± SD age: 10.70 ± 3.29 years</td>
<td>16 patients in the flunarizine group experienced a &gt; 50% decrease in frequency and duration of migraine attacks as compared to 3 patients in the placebo group. 3 patients in the flunarizine group discontinued due to drowsiness, fatigue, and gastrointestinal complaints. The most frequently AEs were sleepiness and weight gain.</td>
</tr>
<tr>
<td>F. Sorge 1988</td>
<td>Flunarizine/Migraine</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>Placebo</td>
<td>Double-blind, placebo-controlled, crossover study/12 weeks</td>
<td>70/70</td>
<td>(5 - 11 years)</td>
<td>Reduction of frequency and duration of migraine attacks was seen after 1 to 2 months of flunarizine treatment. Drowsiness observed in 6 (1 withdrawal) patients (9.5%), and weight gain observed in 14 patients (22.2%)</td>
</tr>
</tbody>
</table>
III.4.1 Methodology

The 2 pivotal studies were randomized, placebo controlled and double blind. One was a parallel group study that included 48 patients (24 on flunarizine and 24 on placebo) and the other was a crossover study that included 70 patients. Patients in this study were randomly assigned to either group A or B. Group A (n=35) received flunarizine as a daily 5-mg dose for 12 weeks, followed by a 4-week washout period and a 12-week daily placebo period. Group B (n=35) received placebo for 12 weeks, followed by a 4-week washout period, and then received a 5-mg daily flunarizine dose for 12 weeks.

III.4.2 Efficacy

Results of the parallel group study showed that 16/24=67% patients in the flunarizine compared to 4/24=17% patients in the placebo group experienced a > 50% decrease in the frequency and duration of migraine attacks (difference = 50%; 95% CI: 22% - 68%). In the flunarizine group, the mean percentage reduction of headache frequency was 65.94% (p < 0.001), while it was 32.47% in the placebo group (p < 0.01). The difference amounts to 33.5% (95% CI: 6.9%, 60.2%). The mean reduction in headache duration was 51.05% (p < 0.05) in the flunarizine group and 16.62% (not significant) in the placebo group. The difference amounts to 34.4% (95% CI: 9.5%, 59.4%).

Results of the crossover study showed that in group A, the frequency of migraine attacks decreased significantly (p < 0.001) as compared to baseline from the 3rd month of treatment and remained low throughout the study. In group B, the frequency of migraine attacks decreased significantly (p < 0.001) from the 6th month of treatment on, which corresponds to the 1st month of flunarizine treatment, and remained low throughout the study (see figure below).

Thirty three children (out of 35) in group A and 30 (out of 35) in group B completed the study. Two children in group A discontinued the study during the flunarizine phase: one due to excessive day time sedation, the other due to lack of efficacy. Five patients in group B discontinued the study during the placebo phase due to lack of efficacy. The article does not indicate how dropouts were handled in the analysis.

With respect to methodology, the inclusion criteria, duration, and endpoint used in the studies were as indicated in the guideline, and are therefore adequate.
Although reporting of results in the articles is incomplete (i.e. only significance levels are reported in the crossover study), the efficacy results seem sufficiently convincing for children.

### III.4.3 Safety

In the parallel group study 3 patients in the flunarizine group (3/24=12.5%) discontinued the treatment because of adverse events (AEs; drowsiness, gastrointestinal complaints, and fatigue). The most frequently observed AEs in patients completing the study were sleepiness, observed mainly during the first month, and slight weight gain, observed in 6 patients.

In the crossover study the most frequently observed AEs were weight gain, observed in 14 patients (22.2%) and drowsiness, observed in 6 patients (9.5%). One patient in group A discontinued the study during the flunarizine phase due to excessive daytime sedation.

The number of patients included is small (i.e. 48 and 70 in the studies, respectively). In addition, the treatment guideline of the NVN regarding headache in reviewing the evidence for migraine prophylaxis including the above 2 studies by Sorge et al. (1985 and 1988) suggests that it is uncertain whether these two studies included partly overlapping research population. This is especially a concern with respect to ability of such a small evidence base to detect safety signals, particularly the more rare ones.

The increase in weight is of particular concern also in light of the results of the pharmacodynamic studies showing increases in prolactin and leptin. These results suggest greater safety problems related to these increases, on the long-run and when a larger number of patients, including adolescents, are exposed to flunarizine. Expected problems are amenorrhea, galactorrhea, and sexual dysfunction. Increased prolactin levels can, on the long-term, adversely effect sexual development, fertility, growth and diabetes.

The AEs related to sedation also raise concern with respect to potential effects on cognitive development. The guideline on migraine studies requires evidence from long-term safety studies with special attention to effects on growth, endocrine development, and on cognitive development, especially if the compound has shown to have short-term effect on sedation and alertness. The lack of such evidence in this dossier is considered an important gap which does not enable to ascertain the extent of the safety problem with respect to these important safety signals. Altogether, although the results of the PD studies are inconclusive and the number of AEs in the clinical studies is not always specified, it seems that there are various signals pointing to potential safety problems associated with flunarizine and that the available safety database is insufficient to ascertain the actual safety and hence does not provide reassurance regarding these safety signals.

**EudraVigilance database**

A search in the EudraVigilance database shows that weight gain (n=4), dyskinesia (n=1), extrapyramidal disorder (n=3), depression (n=13), suicidal ideation (n=3) and suicide (attempts) (n=3) have been reported for patients <18 years using flunarizine (period 2000-2015, patient age <18 years, total number of reported ADRs=212). The actual number of reports might be higher, as reporters do not always fill out the age field. Considering the low number of reported ADRs and the lack of information on possible comedication, no conclusion can be drawn from these data and these data were not taken into further account.

### III.4.4 Supportive studies

**Active comparative studies**

Of the 4 active comparative studies 2 were double blinded. Three of the 4 studies used non-registered active comparators (only propranolol is registered for migraine prophylaxis in children). Results showed similar efficacy of flunarizine and the active comparators. Safety results showed weight gain, increased appetite, somnolence, drowsiness and paresthesia in the flunarizine treated patients.
Strictly speaking, similar efficacy of flunarizine and the non-registered active comparators cannot be viewed as supportive of efficacy. However, the study by Lütschg (1990) suggests similar efficacy of flunarizine and propranolol providing supportive evidence for efficacy.

The safety results, showing again increases in weight and somnolence, support the safety concerns that arose in the pivotal studies. The four active comparative studies are presented in the table below.
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Product/indication</th>
<th>Dosage</th>
<th>Comparator</th>
<th>Report type / treatment duration</th>
<th>No. of patients flunarizine/total (age range)</th>
<th>Efficacy results</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Potthann 1987</td>
<td>Flunarizine /migraine</td>
<td>5 mg/day if &lt; 40 kg 10 mg/day if &gt; 40 kg No mg/kg/day provided</td>
<td>Acetylsalicylic acid (ASA) 100 mg/day if &lt; 40 kg 200 mg/day if &gt; 40 kg</td>
<td>Double-blind, comparator-controlled study / 3 months</td>
<td>15/30 (7 - 17 years)</td>
<td>Both treatments efficiently reduced the frequency of headache attacks.</td>
<td>The most common AEs were slight body weight gain in the flunarizine group and abdominal pain in the ASA group. The incidence of AEs in both groups was not statistically different.</td>
</tr>
<tr>
<td>M. Castellana 1989</td>
<td>Flunarizine /migraine</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>Nimodipine 5 x 10 mg/day</td>
<td>Open-labelled, comparator-controlled crossover study / 30 days of treatment for each drug</td>
<td>35/35 (8 - 10 years)</td>
<td>Both drugs were similar in effectively reducing the frequency of attacks and the intake of analgesics. A &gt; 50% reduction in attack frequency was observed in 64% of the patients. 7 patients were non-responder to nimodipine and 3 subjects to flunarizine.</td>
<td>Only moderate AEs were observed. 4 patients reported drowsiness during flunarizine treatment and 2 patients reported flushing during nimodipine treatment.</td>
</tr>
<tr>
<td>L. Lastra Martinez 1990</td>
<td>Flunarizine /migraine</td>
<td>10 mg/day No mg/kg/day provided</td>
<td>Dihydroergotamine final dose of 5 x 1.5 mg/day</td>
<td>Open-labelled, comparator-controlled study / 6 months</td>
<td>25/50 (3 - 13 years)</td>
<td>Dihydroergotamine efficiently reduced the frequency and intensity of headaches but not their duration. Flunarizine efficiently reduced the frequency, intensity, and duration of the headaches. No statistical difference in efficacy was found between the two drugs.</td>
<td>3 patients (12%) experienced AEs in the dihydroergotamine group (abdominal pain and paresthesia), and 5 patients (20%) experienced AEs in the flunarizine group (somnolence, increase in appetite, weight gain, and paresthesia).</td>
</tr>
</tbody>
</table>
### Uncontrolled studies

Two uncontrolled trials were submitted.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Product / indication</th>
<th>Dosage</th>
<th>Comparator</th>
<th>Report type / treatment duration</th>
<th>No. of patients flunarizine/ total (age range)</th>
<th>Efficacy results</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Lütschg 1990</td>
<td>Flunarizine / migraine</td>
<td>5 mg/day if &lt; 25 kg 10 mg/day if &gt; 25 kg No mg/kg/day provided</td>
<td>Propranolol 10 mg/day if &lt; 25 kg 20 mg/day if 25 - 35 kg 40 mg/day if &gt; 35 kg</td>
<td>Double-blind, comparator-controlled study / 4 months</td>
<td>17/33 (3 - 15 years)</td>
<td>A reduction in the number of migraine attacks was observed in 75% of the flunarizine group and in 73.8% of the propranolol group. Propranolol also reduced the severity of attacks.</td>
<td>Transient AEs were observed in 3 of 17 patients of the flunarizine group and in 5 of 15 patients of the propranolol group. The most frequent AE was increased fatigue, which required interruption of therapy in 2 patients of the propranolol group.</td>
</tr>
<tr>
<td>A. Visudhibban 2004</td>
<td>Flunarizine / migraine</td>
<td>14 patients: 5 mg/day 7 patients: 10 mg/day No mg/kg/day provided</td>
<td>None</td>
<td>Open-label, uncontrolled study / 6 months</td>
<td>21/21 (7-15 years)</td>
<td>14 patients (66.7%) experienced an improvement. All of them had a decrease in the frequency of migraines and 3 of them had a shorter duration and a decrease in intensity of migraine attacks. The remaining 7 patients (33.3%) saw no improvement.</td>
<td>No AEs were reported.</td>
</tr>
<tr>
<td>G. Boccia 2006</td>
<td>Flunarizine / gastrointestinal disorders in migrainous children</td>
<td>5 mg/day No mg/kg/day provided</td>
<td>None</td>
<td>Open-label, uncontrolled study / 2 months</td>
<td>10/10 Mean = SD age: 8.63 = 2.8 years</td>
<td>Flunarizine treatment effectively reduced frequency and duration of migraine attacks.</td>
<td>No relevant AEs were reported</td>
</tr>
</tbody>
</table>
Other supportive studies
In four retrospective studies AEs that were encountered included weight gain, somnolence, sedation, increased appetite, depression, drowsiness, and dizziness.
One study for the indication vestibular vertigo was submitted. No new AEs were encountered in this study.

III.5 Discussion on the clinical aspects
Altogether, the efficacy results in the pivotal studies seem sufficiently convincing for children. Results of one of the pivotal studies showed 67% responders (> 50% decrease in the frequency and duration of migraine attacks) in the flunarizine treated groups compared to 17% in the placebo group (difference = 50%; 95% CI: 22% - 68%).
However, there are major doubts with respect to safety. The most common AEs reported in the 2 pivotal studies are weight gain, drowsiness and sedation. Unfortunately, frequencies of these events were not reported in the published articles. These AEs also emerge in the supportive studies with the addition of depression in one of the retrospective (supportive) studies. The increase in weight is of particular concern also in light of the results of the PD studies showing increases in prolactin and leptin.
The AE depression was encountered in one of the supportive studies and is also mentioned as a potential AE in the current SmPC of flunarizine. Depression can be a serious AE in children and adolescents which raises a serious concern. One reason for the concern is the risk of suicidality which is associated with depression and is especially high in adolescents.
The AEs related to sedation also raise concern with respect to effects on cognitive development. The guideline on migraine studies requires evidence from long-term safety studies with special attention to effects on growth, endocrine development, and on cognitive development, especially if the compound has shown to have short-term effect on sedation and alertness. The lack of such evidence in this dossier is considered an important gap which does not enable to ascertain the extent of the safety problem with respect to these important safety signals.
In addition, the SmPC of flunarizine indicates that extrapyramidal symptoms (EPS) are a potential safety problem in adults and although this AE was not seen in the submitted studies, this may be due to the small number of patients included and the possibility that with larger numbers EPS will appear cannot be ruled out. EPS in children and adolescents is a serious concern.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This variation application was discussed in the Board meetings of 12 February 2014, 4 June 2015 and 26 November 2015. The Board concluded that the benefit-risk balance of flunarizine in the prophylactic treatment of migraine in children and adolescents is considered negative. There are concerns regarding the effects of increased prolactin, weight gain, effects on growth and sexual maturation, sedation and effects on cognitive development, emergence of depression and associated risk of suicide and emergence of extrapyramidal symptoms.

The submitted dossier suffers from important gaps in evidence in terms of small number of patients included in the studies, the lack of evidence regarding safety (in adolescents) and the lack of long-term safety data.

The Board concluded that the proposed addition of dose instructions for children and adolescents to section 4.2 of the SmPC is not approvable. Instead the MAH was requested to specify in SmPC section 4.1 that Sibelium is only indicated in adults. The variation procedure was finalised on 23 December 2015. The resulting changes to the SmPC are presented below.

V. CHANGES IN PRODUCT INFORMATION

In SmPC section 4.1 it has been specified that Sibelium is only indicated in adults. In addition, a statement was added to section 4.2 and 4.4 of the SmPC that Sibelium is not indicated for use in children and adolescents <18 years, because there are doubts about the safety in this age group. The package leaflet was adapted accordingly.

The changes to SmPC in the context of this variation are presented below, in Dutch. Added text is underlined, strike-through text was deleted.

- **SmPC**

4.1 Therapeutische indicaties

**Volwassenen:**
- Profylaxe van migraine bij patiënten met frequente en ernstige aanvallen, die niet voldoende op een andere behandeling hebben gereageerd of bij wie een andere therapie tot niet aanvaardbare bijwerkingen aanleiding gaf.
- Symptomatische behandeling van vestibulaire vertigo ten gevolge van een vastgestelde functiestoornis van het vestibulaire systeem.

4.2 Dosering en wijze van toediening

*Pediatrische patiënten (jonger dan 18 jaar)*

Sibelium is niet geïndiceerd voor gebruik bij kinderen en adolescenten (zie rubriek 4.4).

4.4 Bijzondere waarschuwingen en voorzorgen bij gebruik

*Pediatrische patiënten*

Sibelium dient niet gebruikt te worden bij kinderen en adolescenten jonger dan 18 jaar, aangezien er twijfels zijn over de veiligheid in deze leeftijdsgroep.
Literature references


Lütschg J. and Vassella F. Behandlung der kindlichen migraene mit flunarizin bzw. propranolol. Schweizerische Medizinische Wochenschrift 120, p.1731-1736, 1990. LMD77442


