NICE advice

Migraine prophylaxis: flunarizine

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in September 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Flunarizine is a calcium channel blocker that reduces smooth muscle spasm. Overall, the studies included in this evidence summary suggest that flunarizine is as effective as propranolol or topiramate at reducing the frequency of migraines in adults. In children, flunarizine was more effective than placebo at reducing migraine frequency, and as effective as nimodipine, aspirin, propranolol or dihydroergotamine. However, all of the studies in children were small and of poor quality. The most common adverse effect of flunarizine is weight gain.

Regulatory status: unlicensed. This topic was prioritised because of the potential clinical

impact of long-term prescribing in primary care.

Effectiveness	Safety
• In 1 RCT (n=783 adults), flunarizine was as effective as propranolol, each reducing the mean migraine frequency from around 3 at baseline to around 2 per 4 weeks (calculated over the 16-week study duration). • In a 16 week study conducted in primary care (n=434 adults), frequency of migraine attacks was reduced in 54.5% of people in the flunarizine group and 53.1% of people in the propranolol group. In an outpatient study (n=87 adults), frequency of migraine attacks was reduced in 67.9% of people in the flunarizine group and 45.8% of people in the propranolol group. No statistical analysis was reported in either study. • Another RCT (n=150 adults), compared flunarizine, topiramate, and their combination. At 1 year it found no statistically significant difference in the proportion of people who had at least a 50% reduction in mean monthly migraine frequency compared with baseline. • A Cochrane review in children and young people aged 3 to 17 years included 2 RCTs comparing flunarizine with placebo and 4 RCTs comparing flunarizine with an active comparator. Flunarizine reduced migraine frequency more than placebo and to a similar degree to the active comparators, although all of these studies were small and of poor quality.	• Flunarizine is contraindicated in people with current depressive illness, a history of recurrent depression, pre-existing symptoms of Parkinson's disease or other extrapyramidal disorders (Sibelium; Irish summary of product characteristics [SPC]). • Flunarizine should be used with caution in older people, and people taking flunarizine should be assessed at regular intervals for the development of extrapyramidal symptoms or the symptoms of depression (Sibelium; Irish SPC). • Accumulation may occur at higher than recommended doses, with an increased incidence of adverse effects (Sibelium; Irish SPC).

Patient factors	Resource implications
• Weight gain is a very common (1 in 10 or more) adverse effect (Sibelium; Irish SPC). • For maintenance treatment, 2 successive drug-free days every week are recommended and flunarizine should be stopped after 6 months and only re-started if the person's condition relapses (Sibelium; Irish SPC).	• No price is listed for flunarizine and the cost will differ depending on the source. NHS prescription cost analysis for England 2013 reported that flunarizine hydrochloride 5 mg capsules cost £115.42 per item (with the average quantity per item of 68.92). • The cost of alternative treatment options for migraine prophylaxis (not all of which are licensed specifically for this use) varies depending on the treatment used and the dosage. Propranolol tablets 40 mg 3 times a day costs £9.06 for 30 days' treatment. Topiramate tablets 50 mg twice a day cost £3.52 for 30 days' treatment.

Introduction and current guidance

The NICE guideline on the diagnosis and management of headaches in young people and adults makes recommendations on diagnosing and managing the most common primary headache disorders in young people (aged 12 years and older) and adults. It states that headaches are 1 of the most common neurological problems presenting to GPs and neurologists. The most common primary headache disorders are tension-type headache, migraine and cluster headache. For migraine with or without aura, the NICE guideline recommends that the benefits and risks of prophylactic treatment should be discussed with the person taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life.

NICE recommends that topiramate or propranolol should be offered for the prophylactic

treatment of migraine according to the person's preference, comorbidities and risk of adverse events, with other treatments recommended if both of these are unsuitable or ineffective.

Full text of Introduction and current guidance.

Product overview

Flunarizine is a calcium channel blocker that reduces arterial and arteriolar smooth muscle spasm. While flunarizine is unlicensed in the UK, it is licensed in other countries, including Ireland, for the prophylaxis of migraine in adults aged 18 years and older. For adults aged 18 to 64 years the starting dose is 10 mg at night, and for adults aged 65 years and older the starting dose is 5 mg at night (Sibelium summary of product characteristics; Janssen-Cilag).

Full text of Product overview.

Evidence review

- This evidence summary is based on 4 studies and a Cochrane review. Two of the studies were randomised controlled trials (RCTs): Diener et al. (2002) compared flunarizine with propranolol, and Luo et al. (2012) compared flunarizine, topiramate, and a combination of the two. The other 2 studies were identically designed double blind studies that compared flunarizine with propranolol (Lucking et al. 1988); it is unclear if these 2 studies were randomised. The Cochrane review (Victor et al. 2003) evaluated drug treatment for the prevention of migraine in children and young people. This was last updated in December 2002 and is not planned to be reviewed.

- Diener et al. (2002) was an RCT conducted in 8 European countries. It compared the safety and efficacy of flunarizine at 2 different doses with propranolol over a 16-week period. The study included 810 adults aged 18 to 65 years with a history of migraine for at least 1 year. For the intention-to-treat (ITT) population, flunarizine 10 mg daily (with 2 consecutive 'drug-free' days from week 9 onwards) and flunarizine 5 mg daily were reported to be at least as effective as propranolol 160 mg daily for the efficacy outcome of mean migraine frequency per 4 weeks ($p<0.001$ in one-sided equivalence test; each group reduced the mean migraine frequency from around 3 at baseline to around 2 per 4 weeks). For the percentage of responders per 4 weeks for the ITT population, flunarizine 10 mg daily was reported to be at least as effective as

propranolol (p=0.01 in one-sided equivalence test) but flunarizine 5 mg daily was not (p=0.344 in one-sided equivalence test). It is unclear if Diener et al. (2002) was a non-inferiority study or an equivalence study, and results from both the ITT population and the per protocol population would be needed to support this finding. The per protocol analysis was not presented.

- Lucking et al. (1988) compared flunarizine 10 mg daily with propranolol 40 mg 3 times a day over a 16-week period in 2 identically designed double-blind studies in Germany in adults with a history of migraine. The first study included 87 people recruited from 12 hospital outpatient departments and the second study included 434 people recruited from 99 medical practices in primary care. In the primary care study, the frequency of migraine attacks was reduced in 54.5% of people in the flunarizine group and 53.1% of people in the propranolol group after 4 months of treatment. In the outpatient department study, the frequency of migraine attacks was reduced in 67.9% of people in the flunarizine group and 45.8% of people in the propranolol group after 4 months of treatment. No statistical analysis was presented.

- Luo et al. (2012), an RCT conducted in China, compared flunarizine 5 mg daily alone with topiramate 25 mg to 100 mg daily alone and topiramate and flunarizine combined over a 12-month period in 150 adults aged 18 to 65 years with a history of migraine for at least a year. The proportion of people who had at least a 50% reduction in their mean monthly migraine frequency compared with baseline (the primary outcome) was 66.7% (26/39) in the flunarizine group, 72.7% (32/44) in the topiramate group and 76.7% (33/43) in the combined group. There was no statistically significant difference between the 3 groups (p=0.593).

- Diener et al. (2002) and Luo et al. (2012) only included people aged 18 to 65 years. There is limited evidence available for people outside of this age range. The majority of people in the studies were female, however this reflects the higher prevalence rate of migraine in women. None of the studies was conducted in the UK and therefore may not be applicable to UK practice. The results of these studies may also not be applicable to people whose migraine has not responded to a number of different prophylactic treatments already.

- A Cochrane review (Victor et al. 2003) included 2 RCTs that compared flunarizine with placebo and 4 RCTs that compared it with an active comparator. All of the studies were conducted in children and young people aged 3 to 17 years, but were small and of poor quality. There was a statistically significant reduction in migraine frequency with flunarizine compared with placebo in the 2 RCTs that compared flunarizine with placebo. In the 4 RCTs that compared flunarizine with an active comparator

(propranolol, aspirin, nimodipine or dihydroergotamine), there was no statistically significant difference between flunarizine and the other treatments for reduction in migraine frequency.

- The Irish summary of product characteristics for flunarizine dihydrochloride 5 mg tablets (Sibelium; Janssen-Cilag) states that flunarizine is contraindicated in people with a current depressive illness or with a history of recurrent depression and in people with pre-existing symptoms of Parkinson's disease or other extrapyramidal disorders. Weight gain is reported as a very common (1 in 10 or more) adverse effect; common (1 in 100 or more to less than 1 in 10) adverse effects include rhinitis, increased appetite, depression, insomnia, somnolence, constipation, stomach discomfort, nausea, myalgia, menstruation irregularities, breast pain and fatigue.

Full text of Evidence review.

Context and estimated impact for the NHS

No estimate of the current use of flunarizine for migraine was identified. No price is listed for flunarizine and the cost will differ depending on the source. NHS prescription cost analysis for England 2013 reported that flunarizine hydrochloride 5 mg capsules cost £115.42 per item (with the average quantity per item of 68.92), and that in 2013, 700 items of flunarizine hydrochloride 5 mg capsules were dispensed at a net cost of £77,600. It is not known for which indications these items were prescribed.

Full text of Context and estimated impact for the NHS.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with migraine who are thinking about trying flunarizine.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

The NICE guideline on the diagnosis and management of headaches in young people and adults makes recommendations on diagnosing and managing the most common primary headache disorders in young people (aged 12 years and older) and adults. It states that headaches are 1 of the most common neurological problems presenting to GPs and neurologists.

Headache disorders are classified as primary or secondary. The aetiology of primary headaches is not well understood and they are classified according to their clinical pattern. The most common primary headache disorders are tension-type headache, migraine and cluster headache. Secondary headaches are attributed to underlying disorders and include, for example, headaches associated with medication overuse, giant cell arteritis, raised intracranial pressure and infection.

The NICE guideline provides guidance on the diagnosis of headache and includes advice on features that may need further investigations or referral. The NICE guideline states that migraine (with or without aura) presents with unilateral or bilateral moderate or severe pulsating or throbbing pain that lasts for 1 to 72 hours. It can be aggravated by, or cause avoidance of, routine activities of daily living. Accompanying symptoms include unusual sensitivity to light or sound, or nausea or vomiting. Typical aura symptoms include visual

symptoms such as flickering lights, spots or lines or partial loss of vision; and sensory symptoms such as numbness or pins and needles or speech disturbance. Migraine can be diagnosed as episodic (occurring on less than 15 days a month) or chronic (occurring on 15 or more days a month for longer than 3 months).

For migraine with or without aura the NICE guideline recommends that the benefits and risks of prophylactic treatment should be discussed with the person taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life. NICE recommends that topiramate or propranolol should be offered for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Women and girls of childbearing potential should be warned that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. It should be ensured that they are offered suitable contraception. If both topiramate and propranolol are unsuitable or ineffective, NICE recommends considering a course of up to 10 sessions of acupuncture over 5–8 weeks or gabapentin (up to 1200 mg a day) according to the person's preference, comorbidities and risk of adverse events. For people who are already having treatment with another form of prophylaxis such as amitriptyline, and whose migraine is well controlled, NICE recommends that the current treatment can be continued as needed. People with migraine should also be advised that riboflavin 400 mg daily (not licensed as a medicinal product) may be effective in reducing migraine frequency and intensity in some people. The need for continuing prophylactic treatment should be reviewed after 6 months.

Not all of these products are licensed specifically for migraine prophylaxis in children, young people or adults, and individual summaries of product characteristics should be consulted for details.

Product overview

Drug action

Flunarizine is a calcium channel blocker that reduces arterial and arteriolar smooth muscle spasm (Irish summary of product characteristics: Sibelium; Janssen-Cilag).

Regulatory status

Flunarizine is not licensed in the UK. However, it is licensed in other countries, including Ireland, for migraine prophylaxis.

Flunarizine dihydrochloride 5 mg tablets are licensed in Ireland for the prophylaxis of migraine in adults aged 18 years and older. The Irish summary of product characteristics (Sibelium; Janssen-Cilag) recommends that for adults aged 18 to 64 years the starting dose should be 10 mg daily (taken at night), and for adults aged 65 years and over the starting dose should be 5 mg daily (taken at night). The summary of product characteristics states that if depressive, extrapyramidal or other unacceptable adverse effects occur treatment should be stopped. In addition, it recommends that treatment should be stopped if no significant improvement is seen after 2 months of treatment.

For people whose condition responds to initial treatment, the summary of product characteristics recommends that maintenance treatment should continue at the same daily dose but that there should be 2 successive drug-free days every week. It further recommends that flunarizine treatment should be stopped after 6 months and that it should only be re-started if the person's condition relapses (Irish summary of product characteristics: Sibelium).

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using flunarizine.

Cost

Flunarizine is not licensed in the UK. No price is listed for flunarizine and the cost will differ depending on the source. NHS prescription cost analysis for England 2013 reported that flunarizine hydrochloride 5 mg capsules cost £115.42 per item (with the average quantity per item of 68.92).

Evidence review

This evidence summary is based on 4 studies and a Cochrane review. Two of the studies were RCTs: Diener et al. (2002) compared flunarizine with propranolol and Luo et al. (2012) compared flunarizine, topiramate and flunarizine and topiramate combined. The other 2 studies were identically designed double blind studies that compared flunarizine with

propranolol (Lucking et al. 1988); it is unclear if these 2 studies were randomised. The Cochrane review (Victor et al. 2003) evaluated drug treatment for the prevention of migraine in children and young people. This was last updated in December 2002 and is not planned to be reviewed.

This evidence summary also briefly discusses a systematic review (Pringsheim et al. 2012) in the clinical effectiveness section and a post-marketing surveillance study (De Bock et al. 1996) in the safety and tolerability section.

Clinical effectiveness

Diener et al. (2002)

This randomised controlled trial was conducted in 8 European countries (Belgium, Denmark, Spain, France, Germany, Italy, Portugal and Switzerland). It compared the efficacy and safety of flunarizine at 2 different doses with propranolol over a 16-week period. The study included 810 adults aged 18 to 65 years (median age 37) with migraine for at least 1 year (median 10 years, with a median of 4 attacks per month). Participants had to have had 2 to 6 migraines every month for the 2 months before randomisation. Exclusion criteria included use of treatment for migraine prophylaxis in the previous 2 months, previous unsuccessful use of propranolol or flunarizine at an adequate dose for migraine prophylaxis, a history of depressive illness or extrapyramidal disorders.

After a 4-week, single-blind, placebo run-in period, participants were randomised double-blind to 1 of 3 groups: flunarizine 5 mg daily, flunarizine 10 mg daily or propranolol (80 mg daily in week 1 increased to 160 mg daily from week 2 onwards). The method of allocation described suggests that this was concealed. From week 9 onwards participants in the flunarizine 10 mg daily group had 2 consecutive 'drug-free' days each week (Saturday and Sunday); for these 2 days flunarizine was replaced with placebo. A total of 808 participants had at least 1 dose of study medication.

The participants were given a diary in which all migraine attacks had to be recorded. A migraine attack that ended or was interrupted by sleep and then relapsed within 24 hours was recorded as 1 migraine attack. The primary efficacy outcomes were mean migraine attack frequency per 4 weeks (calculated over the 16-week period), mean migraine attack frequency in the last 28 days of the study, percentage of 'responders' per 4 weeks and percentage of 'responders' in the last 28 days of the study. However, only the 4 week outcomes, not those in the last 28 days were planned. A response was classed as a

reduction of at least 50% in the number of migraine attacks compared with the run-in period. The median number of migraine attacks in the 4-week run-in period was comparable across the 3 groups (2.9 for both flunarizine groups and 2.8 for the propranolol group).

Primary efficacy outcome results were presented for the intention-to-treat (ITT) population (n=783), which consisted of all randomised participants who had taken at least 1 dose of study medication and had a post-baseline efficacy observation period of at least 1 month. For the ITT population the mean attack frequency per 4 weeks was 2.0 (95% confidence interval [CI] 1.8 to 2.2) in the flunarizine 5 mg group (n=259), 1.9 (95% CI 1.7 to 2.1) in the flunarizine 10 mg group (n=265), and 1.9 (95% CI 1.7 to 2.0) in the propranolol group (n=259). The mean attack frequency in the last 28 days of the study was 1.8 (95% CI 1.7 to 2.0) in the flunarizine 5 mg group, 1.6 (95% CI 1.4 to 1.8) in the flunarizine 10 mg group and 1.7 (95% CI 1.5 to 1.9) in the propranolol group. For the mean attack frequency per 4 weeks and in the last 28 days of the study, both flunarizine 5 mg and flunarizine 10 mg were at least as effective as propranolol for the ITT population ($p<0.001$ in one-sided equivalence test).

For the ITT population, the percentage of responders per 4 weeks was 36% (92/259) with flunarizine 5 mg, 44% (116/264) with flunarizine 10 mg and 44% (113/258) with propranolol. The percentage of responders in the last 28 days of the study was 46% (118/259) with flunarizine 5 mg, 53% (141/264) with flunarizine 10 mg and 48% (125/258) with propranolol. For the percentage of responders per 4 weeks and in the last 28 days of the study, flunarizine 10 mg was at least as effective as propranolol ($p=0.01$ and $p<0.001$ respectively in one-sided equivalence tests). However, flunarizine 5 mg was not found to be as effective as propranolol for these 2 outcomes ($p=0.344$ and $p=0.053$ respectively for one-sided equivalence tests).

The per protocol population was described, however no results for the primary outcome measures were presented for this population. It is unclear if Diener et al. (2002) was a non-inferiority study or an equivalence study. However, to establish either non-inferiority or equivalence the analysis of both the ITT population and the per protocol population would need to support this finding. It is also unclear what the study defined the margin of equivalence or non-inferiority to be (see evidence strengths and limitations section).

Lucking et al. (1988)

Lucking et al. (1988) compared flunarizine with propranolol over a 16-week period in 2

identically designed double-blind studies in Germany in adults with a history of migraine. Participants had to have had at least 2 migraine attacks a month or single attacks lasting several days over the past 6 months. The first study included 87 people recruited from 12 hospital outpatient departments, and the second study included 434 people recruited from 99 medical practices in primary care. In both studies, flunarizine was given as a 10 mg dose in the evening and propranolol was given at a dose of 40 mg twice a day for 2 weeks which was then increased to 40 mg 3 times a day. It is unclear if allocation to treatment was randomised or if allocation was concealed. Participants were asked to keep a record documenting the occurrence of each migraine attack (further details not provided). After 1, 2, 3 and 4 months of treatment participants were evaluated and the number, duration and severity of migraine attacks, additional analgesic medication taken and side effects of treatment were documented. The final evaluation included 336 people (flunarizine n=166 and propranolol n=170) from the study conducted in primary care and 69 people (flunarizine n=35 and propranolol n=34) from the study conducted in outpatient departments. The mean age of participants included in the final evaluation was 42 years and 77% were female.

In the primary care study, the mean (standard deviation) number of migraine attacks a month was 6 (6) after 1 month of treatment and 4 (4) after 4 months of treatment with flunarizine, and 6 (6) after 1 month of treatment and 4 (5) after 4 months of treatment with propranolol. No statistical analysis was presented. In the outpatient department study, the mean (standard deviation) number of migraine attacks a month was 6 (6) after 1 month of treatment and 4 (5) after 4 months of treatment with flunarizine, and 5 (6) after 1 month of treatment and 3 (5) after 4 months of treatment with propranolol. No statistical analysis was presented.

In the primary care study, the frequency of migraine attacks was reduced in 54.5% of people in the flunarizine group and 53.1% of people in the propranolol group after 4 months of treatment. No statistical analysis was presented. In the outpatient department study, the frequency of migraine attacks was reduced in 67.9% of people in the flunarizine group and 45.8% of people in the propranolol group after 4 months of treatment. No statistical analysis was presented. In the primary care study, the frequency of migraine attacks increased in 11.7% of people in the flunarizine group and 21.2% of people in the propranolol group ($p<0.05$). In the outpatient department study, the frequency of migraine attacks increased in none of the people in the flunarizine group and 5 (20.8%) people in the propranolol group. No statistical analysis was presented. In addition, the number of participants in the outpatient department study was small (n=87).

Luo et al. (2012)

In this RCT, flunarizine alone was compared with topiramate alone and topiramate and flunarizine combined over a 12-month period in 150 adults aged 18 to 65 years with a history of migraine for at least 1 year. The study was conducted in China. Exclusion criteria included use of medication for prophylaxis of migraine in the past month, use of flunarizine in the past 3 months, poor or no response to more than 2 drug regimens for migraine prophylaxis and a history of depressive illness or extrapyramidal disorders. Participants were randomised to 1 of 3 treatment groups: flunarizine 5 mg daily, topiramate (dose started at 25 mg per day and increased by 25 mg per week to 100 mg per day) or flunarizine and topiramate combined (flunarizine 5 mg daily plus topiramate 25 mg to 100 mg daily). It was unclear if allocation was concealed. Participants had a mean age of 43 years, a mean of about 4.5 migraine days a month, and 71.4% were female. Twenty-four participants dropped out of the study and 126 were included in the efficacy analysis.

Participants kept headache diaries for the duration of the study, recording information such as the number of migraine attacks they had each month and the number of days each month with migraine. The proportion of participants who had at least a 50% reduction in their mean monthly migraine frequency compared with baseline (the primary outcome) at 12 months was 66.7% (26/39) in the flunarizine group, 72.7% (32/44) in the topiramate group and 76.7% (33/43) in the combination group. There was no statistically significant difference between the 3 groups (p=0.593).

Pringsheim et al. (2012)

A systematic review, which assessed the evidence base for drugs used for migraine prophylaxis, included 6 RCTs that compared flunarizine with placebo. Four of these RCTs (n= 20, 29, 35 and 58) were assessed as 'fair' quality by the systematic review, and 2 as 'poor' quality. All 4 of the 'fair' quality studies reported a statistically significant decrease in migraine frequency with flunarizine compared with placebo, but because of clinical heterogeneity they could not be combined in a meta-analysis.

Victor et al. (2003)

A Cochrane review, which evaluated drug treatment for migraine prophylaxis in children and young people, included 2 RCTs that compared flunarizine with placebo. Headache frequency standardised over 28 days was used as the primary outcome measure. This review was last updated in December 2002 and is not planned to be reviewed.

A 12-week, double-blind, parallel-group trial (n=48) in children and young people aged 7 to 14 years compared flunarizine 5 mg daily with placebo. Flunarizine reduced the mean number of migraine attacks over 3 months from 8.66 (standard deviation 2.94) before treatment to 2.95 (2.47) during treatment. Placebo reduced the number of migraine attacks from 9.58 (3.09) before treatment to 6.47 (2.13) during treatment. Flunarizine was shown to statistically significantly reduce migraine frequency compared to placebo (standardised mean difference −1.51, 95% CI −2.21 to −0.82; p<0.001). The number needed to treat (NNT) for a 50% reduction of migraine frequency and duration was 1.75 (95% CI 1.22 to 3.1).

The second placebo-controlled trial included in the Cochrane review was a crossover study (n=70) in children aged 5 to 11 years. Participants were initially randomised to flunarizine 5 mg daily or placebo for 12 weeks, then crossed over to the alternative treatment for 12 weeks after a 4-week washout period. The Cochrane review only included the first part of the crossover study because results from this study showed a clear carry-over effect, in that participants initially randomised to flunarizine experienced continued benefit into the placebo period. This study found that headache frequency was statistically significantly lower with flunarizine than with placebo after 2 and 3 months of treatment (p<0.001). No further analysis of this study was provided by the Cochrane review as results for this study were only reported graphically and could not be independently analysed.

The Cochrane review also included 4 studies that compared flunarizine with an active comparator:

- 1 double-blind parallel-group RCT (n=33) comparing flunarizine with propranolol
- 1 double-blind parallel-group RCT (n=30) comparing flunarizine with aspirin
- 1 open-label crossover RCT (n=35) comparing flunarizine with nimodipine
- 1 open-label parallel-group RCT (n=50) comparing flunarizine with dihydroergotamine.

The RCT comparing flunarizine with propranolol was conducted in children and young people aged 3 to 15 years and compared flunarizine 5 mg or 10 mg daily (depending on bodyweight) with propranolol 10 mg or 20 mg 3 times a day (depending on bodyweight) for 4 months. Thirteen of the 17 participants in the flunarizine group and 12 out of the 15 in the propranolol group showed a greater than 75% improvement in migraine frequency. There was no statistically significant difference between the groups (odds ratio [OR] 0.81, 95% CI 0.15 to 4.4).

The RCT comparing flunarizine with aspirin was conducted in children and young people aged 7 to 17 years and compared flunarizine 5 mg or 10 mg daily (depending on bodyweight) with aspirin 100 mg or 200 mg daily (depending on bodyweight) for 8 weeks. Eleven of the 15 participants in the aspirin group and 10 of the 14 participants in the flunarizine group had a 50% or greater reduction in the frequency of their migraine attacks. There was no statistically significant difference between the groups (OR 0.91, 95% CI 0.18 to 4.64).

Two open-label RCTs were included in the Cochrane review. Flunarizine 5 mg daily was compared with nimodipine 10 mg 3 times a day in an open-label crossover study in children aged 8 to 10 years. Participants were randomised to 30 days of treatment with 1 intervention and were then crossed over to the alternative treatment for 30 days after a 30-day washout period. Nineteen participants (out of the 30 participants who completed the study) in both groups had a greater than 50% reduction in their migraine frequency (OR 1.0, 95% CI 0.35 to 2.86). In the second open-label RCT, flunarizine 10 mg daily was compared with dihydroergotamine (dose increased to 1.5 mg 3 times a day) for 6 months in children aged 3 to 13 years. Flunarizine reduced the mean number of migraine attacks per month from 4.16 (standard deviation 4.01) before treatment to 1.69 (1.94) on treatment, and dihydroergotamine reduced it from 6.4 (4.37) to 2.29 (2.83). There was no statistically significant difference between the groups (standardised mean difference 0.24, 95% CI −0.31 to 0.80).

The Cochrane review concluded that the quality of evidence available for the use of drugs for migraine prophylaxis in children was poor. Meta-analysis was not possible because comparable data from more than 1 study was not available for any of the drugs included in the review.

Safety and tolerability

Summary of product characteristics

The Irish summary of product characteristics (SPC) for flunarizine dihydrochloride 5 mg tablets (Sibelium; Janssen-Cilag; licensed in Ireland for the prophylaxis of migraine in adults aged 18 years and older) states that flunarizine is contraindicated in people with current depressive illness or with a history of recurrent depression, and in people with pre-existing symptoms of Parkinson's disease or other extrapyramidal disorders.

The SPC recommends that flunarizine should be used with caution in older people

because it may give rise to extrapyramidal and depressive symptoms and reveal Parkinsonism symptoms. People taking flunarizine should be assessed at regular intervals for the development of extrapyramidal symptoms or the symptoms of depression. If such symptoms develop it is recommended that flunarizine is stopped.

The SPC states that the recommended dose should not be exceeded. Accumulation may occur at higher than recommended doses, with an increased incidence of side effects.

Weight gain is reported as a very common (1 in 10 or more) adverse reaction in the SPC. Common (between 1 in 100 and 1 in 10) adverse reactions reported in the SPC include rhinitis, increased appetite, depression, insomnia, somnolence, constipation, stomach discomfort, nausea, myalgia, menstruation irregularities, breast pain and fatigue.

Adverse events reported in the trials

In Diener et al. (2002), 33.5% (88/263) of participants in the flunarizine 5 mg group, 32.0% (88/275) in the flunarizine 10 mg group and 27.0% (88/270) in the propranolol group reported adverse events (no statistical analysis presented). Serious adverse events were reported by 0.4% (1/263) in the flunarizine 5 mg group, 1.8% (5/275) in the flunarizine 10 mg group and 0.7% (2/270) in the propranolol group. Study withdrawals due to adverse events were 8.0% (21/263) in the flunarizine 5 mg group, 6.9% (19/275) in the flunarizine 10 mg group and 6.7% (18/270) in the propranolol group (no statistical analysis presented). There was a statistically significant increase in mean weight from baseline in all 3 groups ($p \leq 0.001$). Weight increased by at least 5% from baseline in 23% (60/263) of the flunarizine 5 mg group, 24% (67/275) of the flunarizine 10 mg group and 15% (40/270) of the propranolol group (no statistical analysis presented). Depression was reported in 2.7% (7/263) of the flunarizine 5 mg group, 0.7% (2/275) of the flunarizine 10 mg group and 1.9% (5/270) of the propranolol group (no statistical analysis presented). No extrapyramidal symptoms were seen in any of the study participants.

In Lucking et al. (1988), adverse events were reported by 24.6% (52 people) and 37.2% (16 people) of those taking flunarizine in the primary care and outpatient department studies respectively. Among participants taking propranolol, adverse events were reported by 29.6% (66 people) and 47.7% (21 people) of those in the primary care and outpatient department studies respectively. It was reported that there were no relevant changes in body weight with either flunarizine or propranolol. However, in the outpatient department study weight gain was reported by 11.6% (5 people) in the flunarizine group compared with 6.8% (3 people) in the propranolol group (no statistical analysis presented). Sedation and

fatigue were reported more frequently by people taking flunarizine compared with propranolol in the outpatient department study (23.3% [10 people] compared with 9.1% [4 people]; no statistical analysis presented). However, in the primary care study the reported incidence of sedation and fatigue was the same for both groups (8.1%, 17 people taking flunarizine and 18 people taking propranolol).

In Luo et al. (2012), among people in the flunarizine group, 30.8% (12/39) had an increase in their weight from baseline compared with no people in the topiramate group and 11.6% (5/43) of people in the combined flunarizine and topiramate group. There was a statistically significant mean weight increase from baseline in the flunarizine group of 0.6 kg (95% confidence interval [CI] 0.25 to 0.88; p=0.002). The mean weight change in the topiramate group was −0.9 kg (95% CI −1.32 to 0.52; p<0.001) and in the combined treatment group it was −0.2 kg (95% CI −0.39 to 0.02; p=0.071).

De Bock et al. (1996) was a prospective open-label postmarketing surveillance study conducted in the Netherlands which assessed the risk/benefit ratio of flunarizine compared with propranolol when used for migraine prophylaxis. The study was conducted in primary care and included 116 GPs. Allocation to treatment group was randomised according to prescribing GP using a table of random numbers. GPs were randomised to prescribe either propranolol or flunarizine to people enrolled in the study. The study included 686 people with migraine (mean age 40 years, 76% female); 319 people prescribed flunarizine and 362 prescribed propranolol. The average length of follow-up per person was 9 months. There were 13 people with an incidence of depression during treatment in the flunarizine group compared with 9 people in the propranolol group. The incidence of depression per 1000 patients per year was calculated as 91(95% CI 72 to 110) in the flunarizine group and 55 (95% CI 41 to 69) in the propranolol group. The authors reported that the incidence of depression was significantly higher during treatment with flunarizine compared with during treatment with propranolol, but no further statistical analysis was reported. No extrapyramidal symptoms were seen in any of the people in the study.

The Cochrane review (Victor et al. 2003; last updated in December 2002 and not planned to be reviewed), which evaluated drug treatments for migraine prophylaxis in children and young people, included 2 RCTs that compared flunarizine with placebo. For 1 of the RCTs, the Cochrane review reported that there was no statistically significant difference between the 2 groups for withdrawals due to adverse events. For the second RCT, it was not possible to calculate a risk difference between the 2 groups. In this second study, the most common adverse events were drowsiness and weight gain (reported in 9.5% and

22.2% of the 63 participants who completed the study respectively). The Cochrane review also included 4 RCTs that compared flunarizine with an active comparator. One RCT compared flunarizine with aspirin; in this study, adverse events were reported in 5 participants in the aspirin group and in 8 participants in the flunarizine group. Five participants in the flunarizine group had an increase in weight and appetite compared with 1 participant in the aspirin group. Another RCT compared flunarizine with propranolol; in this study, adverse events were reported in 3 participants in the flunarizine group (2 had increased tiredness, and 1 had breathlessness and difficulties of concentration) and in 5 participants in the propranolol (4 had increased tiredness and 1 had pressure behind the eyes). The other 2 RCTs were both open-label studies: one was a crossover study comparing flunarizine with nimodipine and the other compared flunarizine with dihydroergotamine. For both these studies there was no statistically significant difference between the groups for the number of adverse events reported.

Evidence strengths and limitations

Diener et al. (2002) and Luo et al. (2012) were RCTs that compared flunarizine with 2 drug treatments (propranolol and topiramate respectively) that are licensed for migraine prophylaxis and which are often used in UK clinical practice. The efficacy outcomes used in the studies were patient-orientated outcomes such as reduction in migraine frequency. Luo et al. (2012) was conducted over a reasonable length of time (1 year), but Diener et al. (2002) was conducted over a shorter time period (16 weeks). Lucking et al. (1988) also compared flunarizine with propranolol in 2 identically designed double-blind studies. It is unclear however if these 2 studies were randomised, which may have led to bias.

The average age in the studies ranged from 37 to 43 years, and Diener et al. (2002) and Luo et al. (2012) only included people aged 18 to 65 years. There is therefore limited evidence available for people outside of this age range. The majority of participants in the studies were female, however this reflects the higher prevalence rate of migraine in women. Lucking et al. (1988) used an ad-hoc committee classification from the 1960s to define a diagnosis of migraine. Their inclusion criteria and definition of migraine may not conform to the more established International Headache society criteria that has been in use since the 1990s.

None of the studies was conducted in the UK, and therefore may not be applicable to UK practice. Diener et al. (2002) was conducted in several European countries, Lucking et al. (1988) was conducted in Germany, and Luo et al. (2012) was conducted in China.

In Diener et al. (2002), participants who had a previously unsuccessful response to propranolol or flunarizine were excluded, and in Luo et al. (2012) participants with a poor or no response to more than 2 drug regimens for migraine prophylaxis were excluded. The results of these studies may therefore not be applicable to people whose migraine has not responded to a number of different prophylactic treatments already.

It is unclear if Diener et al. (2002) was a non-inferiority study or an equivalence study. In this study, 2 populations were defined for the efficacy analysis: the intention-to-treat (ITT) population and the per protocol population. For the ITT population, flunarizine 5 mg daily and 10 mg daily were reported to be at least as effective as propranolol for the mean migraine frequency per 4 weeks and the mean migraine frequency in the last 28 days of the study. However, for non-inferiority and equivalence studies, both the ITT analysis and the per protocol analysis should support the finding of non-inferiority or equivalence (Piaggio et al. 2006). The results of the per protocol analysis were not reported. It was also unclear what the study defined the margin of equivalence or non-inferiority to be.

Lucking et al. (1988) did not present statistical analysis for the majority of its outcome measures. It was not reported how participants were allocated to each treatment group and if this was randomised or if allocation was concealed. It was also unclear in Luo et al. (2012) if allocation was concealed, which is a potentially important source of bias.

Victor et al. (2003) was a Cochrane review that evaluated drug treatments for migraine prophylaxis in children and young people. It included 2 RCTs comparing flunarizine with placebo and 4 RCTs comparing flunarizine with an active comparator. All of these studies were small. Two of the RCTs comparing flunarizine with an active comparator were open-label and this could have led to bias. The Cochrane review concluded that the quality of evidence available for the use of drug treatment for migraine prophylaxis in children and young people was poor and that there was an urgent need for properly constructed RCTs in this area.

Context and estimated impact for the NHS

Cost effectiveness

No studies assessing the cost effectiveness of flunarizine for migraine were identified.

The table below gives the costs of alternative treatment options for preventing migraine in

young people (aged 12 years and older) and adults based on treatments recommended in the NICE guideline on the diagnosis and management of headaches in young people and adults.

Table 1 Costs of alternative treatment options for preventing migraine

	Example dosage in adults[a]	Estimated cost for 30 days' treatment (excluding VAT)[b]
Propranolol tablets	40 mg 3 times a day	£9.06
Propranolol modified-release capsules	160 mg once a day	£4.65
Topiramate tablets	50 mg twice a day	£3.52
Topiramate capsules	50 mg twice a day	£47.37
Gabapentin capsules	400 mg 3 times a day	£4.45

[a] Not all of these products are licensed for migraine prophylaxis in children, young people or adults. See summaries of product characteristics for details. The doses shown are example doses and do not represent the full range that can be used, and they do not imply therapeutic equivalence.

[b] Prices based on Drug Tariff August 2014.

Current drug usage

No estimate of the current use of flunarizine for migraine was identified. No price is listed for flunarizine and the cost will differ depending on the source. NHS prescription cost analysis for England 2013 reported that flunarizine hydrochloride 5 mg capsules cost £115.42 per item (with the average quantity per item of 68.92), and that in 2013, 700 items of flunarizine hydrochloride 5 mg capsules were dispensed at a net cost of £77,600. It is not known for which indications these items were prescribed.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with migraine who are thinking about trying flunarizine.

Relevance to NICE guidance programmes

This use of flunarizine is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued a clinical guideline on the diagnosis and management of headache in young people and adults, and a technology appraisal on botulinum toxin type A for the prevention of headaches in adults with chronic migraine.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

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