Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2134

erenumab 70mg solution for injection in pre-filled pen (Aimovig®)

Novartis Pharmaceuticals UK Ltd

8 March 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

erenumab (Aimovig®) is accepted for restricted use within NHSScotland.

Indication under review: for the prophylaxis of migraine in adults who have at least four migraine days per month.

SMC restriction: patients with chronic migraine and in whom at least three prior prophylactic treatments have failed.

In studies in patients with episodic and chronic migraine, erenumab significantly reduced the number of migraine days per month compared with placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of erenumab. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For the prophylaxis of migraine in adults who have at least four migraine days per month.

Dosing Information

The recommended dose is 70mg erenumab by subcutaneous injection every 4 weeks. Some patients may benefit from a dose of 140mg every 4 weeks. Each 140mg dose is given as two subcutaneous injections of 70mg.

Clinical studies have demonstrated that the majority of patients responding to therapy showed clinical benefit within 3 months. Consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter.[1]

Erenumab is intended for patient self-administration after proper training. The injections can also be given by another individual who has been properly instructed. Refer to the summary of product characteristics (SPC) for further details on administration.

Treatment should be initiated by physicians experienced in the diagnosis and treatment of migraine.[1]

Product availability date

10 September 2018

Summary of evidence on comparative efficacy

Erenumab is a human monoclonal antibody which binds to and blocks the calcitonin gene-related peptide (CGRP) receptor. CGRP is a neuropeptide (modulating nociceptive signalling) and a vasodilator associated with migraine pathophysiology. CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief.[1, 2] Erenumab is licensed for the prophylaxis of migraine in adults who have at least four migraine days per month.[1] The submitting company has requested that SMC considers erenumab for the treatment of adult patients with migraine who have at least four migraine days per month and for whom at least three prior prophylactic treatments have failed.

The evidence to support the use of erenumab for the prophylaxis of migraine is based on four clinical studies (STRIVE, ARISE, LIBERTY and Study 295).[3-6] All were randomised, double-blind studies which compared erenumab with placebo over a 12-week double-blind treatment period (24 weeks in STRIVE). STRIVE, ARISE and LIBERTY were phase III study in patients with episodic migraine (defined as ≥4 to <15 migraine days per month and <15 headache days [migraine and non-migraine] per month). Study 295 was a phase II study in patients with chronic migraine (defined as ≥15 headache days per month, of which ≥8 days were migraine days). All studies

enrolled patients aged 18 to 65 years, with ≥12 month history of migraine with or without aura (according to International Classification of Headache Disorders version III [ICHD-III]). Patients were excluded if they had no therapeutic response (no reduction in headache frequency, duration, or severity) to an adequate trial of more than two categories (in STRIVE and ARISE) or more than three categories (in Study 295) of migraine prophylaxis. These were: divalpoex sodium or sodium valproate; topiramate; beta-blockers; tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors; flunarizine or verapamil; and lisinopril or candesartan; and botulinum toxin (Study 295 only). In LIBERTY, patients were required to have failed two to four preventative medicines in terms of efficacy or tolerability.

After screening, eligible patients were randomised, equally in STRIVE, ARISE and LIBERTY and in a 2:2:3 ratio in Study 295, to receive erenumab 70mg, erenumab 140mg or placebo by subcutaneous injection once every 4 weeks during the double-blind phases (note ARISE and LIBERTY did not include erenumab 140mg and 70mg groups, respectively). Randomisation was stratified by geographic area in ARISE, STRIVE and Study 295 and by use of migraine prophylactic medication (current versus previous versus none) in STRIVE and ARISE, by baseline monthly migraine days (MMD, 4 to 7 versus 8 to 14) in LIBERTY and by medication overuse (presence versus absence) in Study 295.[6, 7]

The primary outcome was the change from baseline in mean MMD in all studies except LIBERTY, where it was a secondary outcome. The primary outcome of the LIBERTY study was at least a 50% reduction from baseline in MMD (defined as ≥ 50% responder rate) and this was a secondary outcome in the other studies along with change from baseline in the number of days when acute migraine specific medicines were used. Outcomes were calculated from the each of the last 3 months of the 24-week, double-blind phase in STRIVE and the last 4 weeks of the 12-week, double-blind phase in all other studies. Definitions of migraine days differed between the episodic and chronic migraine studies: qualifying migraine days lasted for ≥30 minutes and ≥4 hours respectively.

Results for primary and secondary outcomes statistically significantly favoured both doses of erenumab compared with placebo in all studies.[6, 7] Details of results are presented in table 1 below.

Table 1: Results of primary and secondary outcomes in the total study populations of the STRIVE, ARISE and LIBERTY (episodic migraine) study and Study 295 (chronic migraine).[3-6]

		Reduction in MMD		**50% Response***		**Reduction in MMUD**	
	N	**LSM**	**Difference (95% CI)**	**%**	**OR (95% CI)**	**LSM**	**Difference (95% CI)**
Study 295 study (in Chronic Migraine)							
Erenumab 70mg	188	-6.6	-2.5 (-3.5, -1.4)	40%	2.2 (1.5, 3.3)	-3.5	-1.9 (-2.6, -1.1)
Erenumab 140mg	187	-6.6	-2.5 (-3.5, -1.4)	41%	2.3 (1.6, 3.5)	-4.1	-2.6 (-3.3, -1.8)
Placebo	281	-4.2		24%		-1.6	

STRIVE study (in Episodic Migraine)							
Erenumab 70mg	312	-3.2	-1.4 (-1.9, -0.9)	43%	2.1 (1.5, 3.0)	-1.1	-0.9 (-1.2, -0.6)
Erenumab 140mg	318	-3.7	-1.9 (-2.3, -1.4)	50%	2.8 (2.0, 3.9)	-1.6	-1.4 (-1.7, -1.1)
Placebo	316	-1.8		27%		-0.2	
ARISE study (in Episodic Migraine)							
Erenumab 70mg	282	-2.9	-1.0 (-1.6, -0.5)	40%	1.6 (1.1, 2.3)	-1.2	-0.6 (-1.0, -0.2)
Placebo	288	-1.8		30%		-0.6	
LIBERTY study (in Episodic Migraine)							
Erenumab 140mg	119	-1.8	-1.6 (-2.7, -0.5)	30%	2.7 (1.4, 5.2)	-1.3	-1.7 (-2.4, -1.0)
Placebo	124	-0.2		14%		0.5	

MMD = monthly migraine days; MMUD = monthly (acute migraine specific) medication use days; LSM = least square means; 95% CI = confidence interval; * 50% response = 50% reduction in MMD. All outcomes assessed at end of double-blind treatment phase compared with baseline.

To support the proposed positioning, the company also presented results from subgroup analyses of patients who had failed at least three previous categories of migraine prophylaxis treatment. These analyses were performed post hoc and included small numbers of patients.[8, 9]

A number of different patient reported outcomes were assessed as secondary or exploratory outcomes during the studies and results favoured erenumab over placebo. The Migraine Specific Questionnaire (MSQ) was an exploratory outcome in STRIVE, ARISE and Study 295. This is a self-administered instrument measuring three dimensions: role function preventive (RFP), role function restrictive (RFR) and emotional function (EF). In the total study populations, results found greater improvement with erenumab compared with placebo which exceeded the minimally important difference for RFR in all studies, RFP in STRIVE and Study 295 (140mg dose groups only) and EF in Study 295.[3, 6, 17] Results from open-label extension studies suggest that the efficacy of erenumab was maintained to week 52.[12 13]

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

In the safety population of the STRIVE study, an adverse event was reported by 57% (180/314), 55% (177/319), and 63% (201/319) of patients randomised to the erenumab 70mg, erenumab 140mg, and placebo groups respectively. Serious AEs were reported by 2.5%, 1.9% and 2.2% of patients respectively. In the erenumab groups, 2.2% of patients discontinued treatment due to an adverse event compared with 2.5% of patients in the placebo group. The most frequently reported adverse events in the erenumab 70mg, 140mg and placebo groups respectively were: nasopharyngitis (9.9%, 11% and 10%), upper respiratory tract infection (6.7%, 4.7% and 5.6%), sinusitis (2.2%, 3.4% and 2.2%), constipation (1.6%, 3.4% and 1.3%), arthralgia (2.2%, 2.2% and 1.9%), fatigue (1.9%, 2.2% and 2.5%), nausea (2.2%, 1.9% and 1.9%), influenza (1.3%, 2.5% and

1.9%), urinary tract infection (1.6%, 2.2% and 2.2%), back pain (1.9%, 1.9%, 2.2%), injection site pain (3.2%, 0.3%, 0.3%),migraine (1.3%, 0.9% and 3.1%) and hypertension (1.6%, 0% and 2.5%).[7]

In the safety population of Study 295, an adverse event was reported by 44% (83/190) of patients in the erenumab 70mg group, 47% (88/188) of patients in the erenumab 140mg group and 39% (110/282) of patients in the placebo group. Serious AEs were reported by 3.2%, 1.1% and 2.5% of patients respectively. An adverse event led to treatment discontinuation in no patients in the erenumab 70mg group, 1.1% of patients in the erenumab 140mg group and 0.7% of patients in the placebo group.[6] The most frequently reported adverse events in the erenumab 70mg, 140mg and placebo groups respectively were: injection site pain (3.7%, 3.7% and 1.1%), upper respiratory tract infection (2.6%, 3.2% and 1.4%), nausea (2.1%, 3.2% and 2.5%), nasopharyngitis (3.2%, 1.6% and 5.7%), constipation (0%, 4.3% and 0.4%), muscle spasm (0.5%, 3.7% and 1.4%) and migraine (1.8%, 2.7% and 1.1%).[6]

The European Medicines Agency (EMA) noted that erenumab constitutes a novel approach for prophylaxis of migraine and that there are limited safety data to assess the theoretical concern that erenumab may aggravate ischemic events such as stroke, transient ischemic attack and myocardial infarction, risks that are already slightly increased in patients with migraine.[2]

Summary of clinical effectiveness issues

Migraines are headaches associated with significant pain and additional symptoms, including nausea, vomiting and light and/or sound sensitivity. They are common and affect approximately 15% of the European population. Migraines are arbitrarily defined as episodic (headaches occurring on less than 15 days per month) and chronic (headaches occurring on 15 or more days per month of which ≥8 are migraine days). The aim of prophylactic therapy is to reduce the number of MMD and so improve daily functioning and quality of life.[2, 14] Current guidelines recommend propranolol as a first-line prophylactic treatment for patients with episodic or chronic migraine. Other recommended treatments include topiramate, amitriptyline, candesartan and sodium valproate. Some of these medicines are used outwith licensed indications. Botox® is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.[14] Erenumab is the first of a new class of medicines for migraine prophylaxis, a CGRP antagonist. The company has positioned erenumab for the treatment of adult patients with migraine and with at least four migraine days per month for whom at least three prior prophylactic treatments have failed. Clinical experts consulted by SMC considered there is an unmet need for disease-specific effective prophylactic treatments for patients with resistant migraine.

The primary outcome in all studies was the change from baseline in MMD, except LIBERTY where it was a key secondary outcome. This was a direct health outcome and results statistically favoured erenumab over placebo. Due to both erenumab doses being assessed, the STRIVE and

Study 295 were considered pivotal by the EMA.[2] A reduction of one monthly headache day has been suggested as the minimal important difference and this was exceeded in all studies. In the episodic migraine studies, MMD reduced from a baseline of approximately 8 to 9 days by a placebo-adjusted 1.0 to 1.4 days with erenumab 70mg and by 1.6 to 1.9 days with erenumab 140mg. In chronic migraine, MMD reduced from a baseline of approximately 18 days by a placebo-adjusted 2.5 days with erenumab 70mg and 140mg.[2, 3, 5-7] The reductions in MMD achieved in all groups in Study 295 (chronic migraine) were greater than in the studies in episodic migraine but the baseline MMD were higher (18 days compared with 8 days) which was considered by the EMA as representative of those migraine populations.[2] In addition, 30% to 50% of erenumab treated patients achieved a 50% reduction in MMD (compared with placebo rates of 14% and 30%) which the EMA considered clinically relevant.[2] The SIGN guideline notes a reduction in migraine headache severity and/or frequency of 30 to 50% is considered successful within clinical studies.[14] Results for the primary outcome were supported by positive effects on secondary outcomes, including the 50% responder rate, reduction of acute migraine-specific treatments and positive effects on quality of life.[2]

Clinical evidence to support the proposed positioning of patients who had failed at least three previous migraine prophylactic treatments was based on post hoc subgroup analyses. In the exclusion criteria of the clinical studies, a lack of therapeutic response was defined as no reduction in headache frequency, duration, or severity after ≥6 weeks at accepted therapeutic dose. Patients were not excluded for insufficient efficacy or poor tolerability. The study randomisation procedures were not stratified for failure of at least three previous migraine prophylactic treatments and although the baseline characteristics appeared broadly similar, there may be imbalances between the resulting subgroups. The studies included patients who were treatment naïve and previously treated and the numbers of patients in the subgroups who had failed at least three previous categories of migraine prophylaxis were small. In addition, a proportion of patients who met the company's proposed positioning were excluded from the studies. Due to their post hoc nature and small numbers of patients, these results should be interpreted with caution. Results from LIBERTY, which included patients unsuccessfully treated with two to four prophylactic medicines, may provide some reassurance about the efficacy of erenumab in the positioning.[5]

The subgroups used in the clinical section of the company submission (those who had failed at least three previous *categories* of migraine prophylactic treatments) were different (very slightly smaller) than the subgroups used in the indirect comparisons economic analyses (who had failed at least three previous migraine prophylactic *treatments*). The company indicated that this difference was due to the availability of data.

Both pivotal studies excluded patients with any major cardiovascular disease including myocardial infarction, stroke, transient ischaemic attacks, unstable angina or revascularisation procedure within the last 12 months and the SPC notes that no safety data are available for these patients. The EMA notes that there is a theoretical concern due to the vasodilating effects of erenumab and potential for long-term use of erenumab as a prophylactic treatment. A non-interventional study on cardiovascular outcomes in patients with pre-existing conditions is to be performed.[1, 2]

There are no active comparative data available, as all studies compared erenumab with placebo. The company considered that best supportive care (BSC) was the relevant comparator in clinical practice for patients with episodic migraine, since there are no other licensed treatments available specifically for patients who have failed at least three previous treatments. In patients with chronic migraine, the company considered Botox® to be a relevant comparator, since it is licensed and accepted for restricted use by SMC. The company performed an indirect comparison, using the Bucher method, to compare erenumab with Botox® in the chronic population. This used results from the subgroup of patients who had failed at least three previous migraine prophylaxis medicines from Study 295 for erenumab and a subgroup from a pooled analysis of the PREEMPT 1 and 2 studies for Botox®. Using the outcome of ≥50% response rate in monthly headache days (MHD), the indirect comparison found no evidence of a difference between erenumab (70mg and 140mg) and Botox®, although the results numerically favoured erenumab. Additional analyses in the total study populations found similar results. The company also compared ≥50% response rate in MMD for erenumab with ≥50% response rate in MHD for Botox® but this was considered less robust given the different outcomes used. A number of limitations affect the validity of the indirect comparison including the post hoc nature of the subgroup analyses used, the lack of availability of baseline characteristics for the PREEMPT subgroup population to assess heterogeneity, and the different time points for assessment of outcomes (12 weeks for erenumab and 24 weeks for Botox®) and its short-term nature.

As the first treatments developed specifically for migraine prevention, clinical experts consulted by SMC consider erenumab and other CGRP antagonists as a therapeutic advancement. Erenumab would offer an additional prophylactic treatment option for patients with resistant migraine for whom there are limited alternatives. Erenumab requires administration by subcutaneous injection every 4 weeks and is intended for self-administration after appropriate training.[1] For some patients with chronic migraine, this self-administration may offer an advantage compared with Botox® which is administered by intramuscular injection at 31 to 39 sites, repeated after 12 weeks.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

A cost-utility analysis was presented comparing erenumab with best supportive care (BSC) in patients who experience ≥4 MMD and for whom ≥3 prior prophylactic treatments have failed. Within this proposed positioning, the cost-effectiveness of erenumab in two further sub-groups is assessed: the chronic migraine population and the episodic migraine population. For the chronic migraine population, Botox® was included as an additional comparator. A health care perspective and a 10-year time horizon were selected in the base case of the economic model.

A decision tree plus Markov model was used, based on a 4-weekly administration of erenumab. A decision tree was used to represent the assessment period of 12 weeks, during which responders were identified using a criteria of a minimum 50% reduction in MMD from baseline. The Markov

model was used to represent the post-assessment period during which responders could transition between 'on treatment' and 'discontinuation' states. The model used a 12- week cycle length.

The key clinical data used in the model were taken from four studies – Study 295, STRIVE, ARISE, and LIBERTY.[3-6] The last three studies involved only episodic migraine patients. An indirect comparison was also conducted to compare erenumab with Botox® in the chronic population. Important model parameters estimated from the trial data were MMD distributions, responder rates, treatment mix and post-assessment rate of negative discontinuation and adverse event rates.

Health-related quality-of-life data were collected using migraine specific patient reported outcomes via the MSQv2.1 in Study 295, ARISE and STRIVE.[4, 6] These patient level data were then mapped onto EQ5D-3L to estimate utility values.

Applicable costs and health resource use data were identified from clinical studies and the National Health and Wellness Survey. The model included erenumab and Botox® unit costs, administration costs, and disease management costs (including cost of prophylactics).

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

The base case analysis for all patients in the proposed positioning (i.e. whole population) presented by the submitting company produced an incremental cost-effectiveness ratio (ICER) of £22,455 per quality-adjusted life-year (QALY) for the blended dose (a 50:50 split between 70mg and 140mg 4-weekly) and an ICER of £19,835 per QALY for the 140 mg dose.

Results for the chronic and episodic migraine sub-groups within the whole population were also provided and are outlined in table 2 below:

Table 2: Results of cost-effectiveness analysis for subgroups within proposed positioning

Sub-group (dose)	Comparator	ICER with PAS
Chronic (blended)	Botox®	£18,883
Chronic (140 mg)	Botox®	£17,823
Chronic (blended)	BSC	£17,217
Chronic (140 mg)	BSC	£13,345
Episodic (blended)	BSC	£35,810
Episodic (140 mg)	BSC	£40,667

The sensitivity and scenario analysis identified that results were most sensitive to the assumptions around MMDs for non-responding patients, as well as the specific definition of response (i.e.50% reduction in MMDs). Selected results from the sensitivity analysis are presented in table 3 below:

Table 3: Selected sensitivity analyses

Scenario	ICER with PAS
Non-response change to 12 week BSC MMDs – in whole population (blended dose) vs BSC	£40,104
Non-response change to 12 week BSC MMDs – in chronic population (blended dose) vs Botox® / vs BSC	£21,272 / £25,334
Non-response change to 12 week BSC MMDs – in episodic population (blended dose) vs BSC	£69,187
Apply 30% responder definition - in whole population (blended dose) vs BSC	£38,227
Apply 30% responder definition - in chronic population (blended dose) vs Botox® / vs BSC	£21,421 / £24,808
Apply 30% responder definition - in episodic population (blended dose) vs BSC	£76,752
Combined scenario – in whole population (blended dose) vs BSC*	£58,164
Combined scenario - in chronic population (blended dose) vs Botox®* / vs BSC**	£31,396 / £33,931
Combined scenario - in episodic population (blended dose) vs BSC**	£78,854

BSC=best supportive care, MMD=monthly migraine days, ICER=incremental cost-effectiveness ratio
* Combined scenario simultaneously varied three key drivers of the model (i.e. non-responders revert to 12-week BSC MMDs, 30% stopping rule; adjustment of blended dose proportion to 70:30 split between 70mg and 140mg)
**Combined scenario simultaneously varied three key drivers of the model (i.e. non-responders revert to 12-week BSC MMDs, 30% stopping rule; adjustment of blended dose proportion to 30:70 split between 70mg and 140mg)

The main weaknesses with the analysis are:

- The base case analysis in the proposed positioning was not informed by pooling data from all four key studies due to differences in outcome definitions. The study populations were broader than the proposed positioning to which this economic model applies and the post-hoc analysis of study data was based on relatively small numbers with a potential for bias.
- There is uncertainty regarding the comparative efficacy of erenumab and Botox® as the indirect comparison between them had several limitations as outlined in the clinical effectiveness section above.
- The assumptions regarding MMD for non-responding patients is a key driver of cost-effectiveness. Non-responding patients were assumed to continue on BSC and maintain the MMD improvement achieved at week 12 until the end of the time horizon. The company considered this to be the most appropriate assumption to make on the basis of a 'regression to mean' argument whereby non-responders would have experienced the reduction naturally over time in the absence of any intervention. Whilst this may be a statistically valid rationale, assuming sustained improvement in MMD (albeit less than the response threshold) for a 10 year period might not be adequately conservative. In the sensitivity analysis, ICERs increased substantially when non-responders were assumed to have MMD identical to that of patients on BSC at 12 weeks or reverted to baseline MMD.
- Results of the economic evaluation were sensitive to the MMD reduction threshold employed when assessing response to erenumab. In the base-case analysis a ≥50% reduction from

baseline MMD was used as a threshold, consistent with the way response was assessed in the clinical studies. However, a lower threshold may be employed in practice, particularly for the most severe patients for whom even a small reduction in MMDs could be viewed as a successful outcome. This could lead to higher rates of erenumab continuation amongst patients achieving lower, yet meaningful, levels of MMD reduction.

- The model only includes one assessment period at the 12 week time point (and 24-week for Botox®). Whist a treatment discontinuation rate has been incorporated into every cycle, the lack of an additional assessment period at a later time point implicitly assumes there is no future gaining or waning of treatment effect. Hence, patients are assumed to maintain the reduction in MMD. This simplifying assumption of a sustained benefit is not sufficiently supported by long term data at present.

Despite the weaknesses outlined above, the economic case has been demonstrated in the chronic migraine population.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from The Migraine Trust and the National Migraine Centre, both organisations are registered charities.

- The Migraine Trust has received 2.3% pharmaceutical company funding in the past two years, including from the submitting company. The National Migraine Centre has received 3% pharmaceutical company funding, including from the submitting company.

- The symptoms associated with migraine attacks are painful and debilitating. They include severe throbbing pain in the head, nausea and vomiting, and sensitivity to light, sound and smell. The high frequency and severity of attacks experienced by chronic migraine sufferers have long-term and substantial impact on day-to-day and work related activities and patients often have decreased quality of life.

- Many of the current prophylactic treatments for migraine are medicines that have been developed for other medical conditions and repurposed for migraine. They often have unwanted side effects and patients may be unable to tolerate them for long enough or at a high enough dose for the medicine to be effective.

- Erenumab is a specific preventative treatment designed for migraine. It is a targeted treatment which seems to be generally well tolerated and easy to use, with the potential

for fewer GP/hospital appointments, fewer side effects and the opportunity for substantial improvement in patient quality of life.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Pharmacological management of migraine; A national clinical guideline (SIGN 155) in February 2018.[14] For the prevention of migraine, this guideline recommends propranolol as a first-line prophylactic treatment for patients with episodic or chronic migraine. Other recommended treatment options to be considered for prophylaxis in patients with episodic or chronic migraine include topiramate, amitriptyline, candesartan and sodium valproate. Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments. The guidance also acknowledges that pizotifen is widely used in clinical practice but that there is a paucity of available evidence.

The National Institute for Health and Care Excellence (NICE) published guidance entitled Headaches in over 12s: diagnosis and management; a clinical guideline (CG150) in September 2012 and the guideline was updated in 2015.[15] The NICE guideline recommends prophylactic treatment of migraine (with or without aura) with topiramate or propranolol and to consider amitriptyline according to patient's preference, comorbidities and risk of adverse events. The use of gabapentin is not recommended.

The British Association for the Study of Headache (BASH) published Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache in January 2010 which was the 3rd edition and 1st revision of the guidance.[16] The guidance highlights that there is a paucity of available evidence regarding the treatment and management of headache and that recommendations are therefore comprised of available evidence as well as expert opinion. First-line prophylactic medicines recommended include beta-adrenergic blockers without partial agonism (atenolol, metoprolol, propranolol or bisoprolol) or amitriptyline. Second-line prophylactic medicines include topiramate or sodium valproate. Third-line prophylactic medicines include gabapentin or methysergide. The guideline notes that Botox® is licensed for prophylaxis of patients with more than 15 headache days per month, of which at least eight days are with migraine.[16]

These guidelines predate the availability of erenumab.

Additional information: comparators

Botulinum toxin type A (Botox®) for the prophylactic treatment of patients with chronic migraine.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Erenumab	**70mg to 140mg every 4 weeks by subcutaneous injection**	**5,024 to 10,049[a]**
Botulinum toxin type A (Botox®)	155 to 195 units every 12 weeks by intramuscular injection	1,382

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 8 January 2019. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. [a] the 140mg dose is currently based on 2 x 70mg injections (a 140mg pre-filled pen is anticipated to be available shortly).

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 February 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.