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General review

Migraine treatment: Position paper of the French Headache Society

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INFO ARTICLE

Keywords:
Migraine
Headache
Guidelines
Recommendations
CGRP
Gepants

ABSTRACT

The French migraine management recommendations were published in 2021. However, in the last three years, new data have come to light and new drugs have been approved (eptinezumab, rimegepant and atogepant) by the European Medicines Agency that require us to take a position on their use and to update certain elements of the recommendations. The first important message concerns the position of the French Headache Society on the use of preventive treatments (monoclonal antibodies and gepants) targeting the calcitonin gene-related peptide (CGRP) pathway. In terms of efficacy and safety, and as suggested by other national headache societies, these treatments can be offered as first-line treatment, although the scope defined by the French national health authority for possible reimbursement is limited to patients with severe migraine, at least eight headache days per month and

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https://doi.org/10.1016/j.neurol.2024.09.008

for whom two previous preventive treatments have failed. Another important change concerns the position of topiramate as a preventive treatment for migraine in women of childbearing age. This treatment has been proposed as a first-line treatment for chronic migraine. However, recent pharmacovigilance data have highlighted a potential adverse effect on neurodevelopment in children exposed in utero. As a result, this treatment is formally contraindicated during pregnancy and must be used with extreme caution in women of childbearing age (effective contraception, no therapeutic alternative available and annual follow-up as with valproate). It can therefore no longer be offered as first-line treatment for women of childbearing age.

Since the publication of the latest French recommendations for the management of migraine in adults, concerning diagnosis [1], drug treatments [2] and non-drug therapies [3], a number of important points need to be clarified. It is important to underline that the management of migraine has evolved considerably in recent years, thanks to improved knowledge of the pathophysiology of migraine. Indeed, the discovery in the 1980s of the key role played by calcitonin gene-related peptide (CGRP) in the development of migraine pain led to the development of new targeted therapies [4,5]: monoclonal antibodies targeting CGRP or its receptor, and non-peptide small molecule CGRP receptor antagonists known as gepants. The main point of this article refers to the position taken by the French Headache Society on the use of the four monoclonal antibodies targeting the CGRP pathway (in alphabetical order, eptinezumab, erenumab, fremanezumab, galcanezumab) and the gepants. With the arrival of atogepant and rimegepant on the French market, these compounds must be positioned in the therapeutic armamentarium. Another very important point concerns the potential neurodevelopmental risk highlighted for topiramate, which was not clearly known when the 2021 guidelines were published and which now justifies extreme caution when using this drug in women of childbearing age. Finally, the marketing discontinuation of flunarizine is specified.

1. New data on monoclonal antibodies targeting the CGRP pathway and the position of the French headache society on their use and reimbursement

1.1. *Update on the place of the four monoclonal antibodies*

As for monoclonal antibodies targeting the CGRP pathway, only three (erenumab, fremanezumab and galcanezumab) were approved by the European Medicines Agency (EMA) for migraine prophylaxis at the time of publication of the 2021 recommendations. Today, eptinezumab is also approved by the EMA with the same indication as the other three, namely prevention of migraine in adults with at least four migraine days per month. Unfortunately for patients, none of these four treatments are reimbursed at the time of writing.

Up to now, fremanezumab and galcanezumab are available in pharmacies. Only eptinezumab, given intravenously every three months, is currently administered in some French hospitals and clinics, generally free of charge for the patient, with a specific status known in French as ''reserve hospitalière''. Each hospital has the choice of whether or not to list new treatments, and decisions are not uniform across all French healthcare establishments. What's more, for hospitals that do provide access to this treatment, only the dose of 100 mg per infusion is available, making it impossible to increase the dosage to 300 mg per infusion for non-responders. Based solely on the efficacy and safety data for antibodies targeting the CGRP pathway, these four treatments can be offered as first-line treatment to all patients presenting with at least four migraine days per month, according to their approval and as proposed by the European Headache Federation [6] and the American Headache Society [7]. In line with EMA decision, prescription is authorized in France under the terms of their approval, i.e. for all patients with at least four migraine days per month. However, the scope defined by the French national health authority (HAS standing for Haute Autorité de santé) for possible reimbursement is limited to patients with *severe* migraine, at least eight headache days per month and for whom two previous preventive treatments have failed. This rule should therefore be respected for patients receiving infusions of eptinezumab with the cost at least partly covered by the hospital supplying the product, but does not apply to patients who are prepared to finance the whole cost of treatment themselves, for galcanezumab and fremanezumab. These rules will also have to be followed for subcutaneous antibodies if they are reimbursed in the coming years. From a medico-economic point of view, a study carried out in the United Kingdom showed that eptinezumab is a cost-effective treatment in patients with four or more migraine days per month and for whom three or more other preventive migraine treatments have failed [8]. Erenumab is also cost-effective for episodic [9] and for chronic [10] migraine.

It is important to note that the notion of *severe* migraine, taken into account in the HAS wording, was proposed in 2021 [11] but that modifications were suggested in 2023 after the criteria were tested in the general patient population (Table 1) [12]. The two new proposals must necessarily be tested in turn in order to validate the best definition.

Table 1 – Definitions of severe migraine.

Initial definition proposed in 2021 [11]	Headaches fulfilling either criterion A or criterion B for at least three months A. Headache frequency of at least eight migraine days per month B. Headache frequency < 8 migraine days per month, but associated with at least one of the following criteria: 1. Headache impact test-6 (HIT-6) score ≥ 60 2. Necessitating complete interruption of activity for 50% of headaches
Modified definition proposed in 2023 [12] Proposal 1	Headaches fulfilling either criterion A or criterion B for at least three months A. Headache frequency of at least eight migraine days per month B. Headache frequency < 8 migraine days per month, but associated with *both* of the following criteria: 1. HIT-6 score ≥ 60 2. Necessitating complete interruption of activity for 50% of headaches
Modified definition proposed in 2023 [12] Proposal 2	Headaches fulfilling either criterion A or criterion B for at least three months A. Headache frequency of at least eight migraine days per month B. Headache frequency < 8 migraine days per month but associated with a HIT-6 score ≥ 65

As with any patient for whom a preventive treatment is prescribed, a comprehensive management program should be applied to assess the frequency of migraine days (using an agenda), the impact of migraine on quality of life (e.g. using the HIT-6 scale), and any comorbid anxiety or depression (e.g. using the HAD questionnaire).

1.2. *Update on efficacy*

Up to now, there have been no randomized controlled trials directly comparing the four monoclonal antibodies. Indirect comparisons did not reveal any significant difference in efficacy between these four compounds [13]. However, it is important to note that response (or non-response) to one antibody is not predictive of response to another. Indeed, it has been shown that the switch from erenumab to another CGRP-mAb led to a ≥ 30% response in more than one-third of the patients [14,15]. In addition, half of the non-responders to anti-CGRP mAbs at 12 weeks may be late responders according to an open-label study, which would justify, at least in some cases, evaluating efficacy at 24 weeks and extending therapy beyond 12 months [16]. Real-world data provides a better understanding of the proportion of patients who continue to benefit from treatment after it has been stopped [17].

Studies directly comparing anti-CGRP monoclonal antibodies with conventional treatments are scarse. One study demonstrated that erenumab was better tolerated than topiramate. A secondary endpoint compared the efficacy of the two treatments [18]. It clearly showed that erenumab was superior for both tolerance and efficacy. When it comes to indirect comparisons, they all point to a much better tolerability of this new therapeutic class compared with conventional treatments, particularly topiramate [13]. In terms of efficacy, the data are less clear, with some meta-analyses showing that topiramate is at least as effective as monoclonal antibodies [19], while others support the superiority of antibodies [13]. In addition, it has recently been shown that using CGRP mAbs earlier in the treatment of migraine patients is more effective than offering another oral medication [20].

Regarding factors predicting response to monoclonal antibodies targeting the CGRP pathway, a meta-analysis showed that a good response to triptans and unilateral pain with or without unilateral autonomic symptoms are predictors of a good response to these drugs [21]. Conversely, obesity, interictal allodynia, higher migraine frequency, greater disability at baseline, a higher number of unsuccessful previous prophylactic medications and psychiatric comorbidities including depression are predictive of a poor response to monoclonal antibodies targeting the CGRP pathway [21,22]. It is important to emphasise that poor response does not mean absence of response. Treatments targeting the CGRP pathway should be considered in patients who may benefit from treatment despite predictors of poor response. For example, in a large French series of patients who had failed all previously available treatments (an average of 11 treatments tried), the introduction of erenumab treatment resulted in a 50% response in just over one in two patients [23].

To date, there is insufficient evidence to support or reject the efficacy of combining treatments targeting the CGRP pathway with oral migraine prophylactic agents [24]. Some real-life data are beginning to emerge concerning the combined use of an anti-CGRP antibody and botulinum toxin type A [25]. There seems to be a benefit to this type of combination, provided access to these therapies is available.

1.3. *Update on treatment duration and tolerance*

A large proportion of patients experience a significant worsening of their migraine frequency after stopping treatment, justifying resumption of treatment [26–28]. It therefore seems important to consider the possibility of long-term treatment for the majority of patients. Long-term efficacy of anti-CGRP antibodies is as good as short-term efficacy [29]. In the context of long-term treatment, the safety profile of these treatments still appears to be very good. However, there is a risk of arterial hypertension, which should be monitored in all patients [30,31]. A risk of Raynaud's phenomenon has been identified [32] and a rare risk of alopecia has also been described [33]. A number of other potential adverse effects have been reported, including sexual dysfunction in both men [34] and women [35] and impaired wound healing [36]. It is important that clinicians pay close attention to these potential side effects to confirm whether they exist, even if they are very rare. On the other hand, the initial data available on exposure during pregnancy is reassuring, although the data is limited and does not yet allow us to recommend the use of these antibodies during pregnancy [37]. The risk of constipation and allergy is confirmed [38].

1.4. *Position of the French Headache Society on reimbursement*

Despite the safety and efficacy data presented above, and despite European marketing authorization, at the time of writing this article, these drugs are not reimbursed in France. Fig. 1 provides a simplified overview of the main elements involved in making a medicine available and reimbursed on the French market. For the four monoclonal antibodies (Table 2), the HAS concluded that the medical benefit (SMR for *service médical rendu*) is important in the preventive treatment of patients with severe migraine with at least eight migraine days per month, for whom at least two prophylactic treatments have failed and who have no cardiovascular problems (patients who have had a myocardial infarction, stroke, transient ischemic attack, unstable angina or coronary artery bypass surgery). At the same time, the HAS Transparency Commission concluded that there was no improvement in the medical benefit (ASMR V for *absence d'amélioration du service médical rendu*) compared with existing treatments. This decision was made in the absence of a direct comparative trial against a reference treatment (beta-blocker or topiramate or candesartan or amitriptyline). Reimbursement of the four monoclonal antibodies is therefore possible, provided that treatment costs are reduced. With reference treatments such as topiramate or beta-blockers costing less than €10 a month, it would seem difficult to offer a monoclonal antibody at a lower cost. On the other hand, the Commission's conclusion that these molecules offer no therapeutic advances is highly questionable. Indeed, all these molecules have shown efficacy even in patients for whom two to four prophylactic treatments had failed. Moreover, it is not technically feasible to conduct a therapeutic trial against a reference treatment in patients who have had two to four failed reference prophylactic treatments. The data available (in randomized clinical trials and in real-world studies) for the four antibodies in these populations therefore show that these treatments represent a breakthrough in these difficult-to-treat patients [39–42].

In conclusion, the four monoclonal antibodies targeting the CGRP pathways are effective and well tolerated and should be offered to patients who need them. Taking into account only the EMA approval and the efficacy and safety data, it should be possible to offer these treatments targeting the CGRP pathways as first-line treatment for all patients who need preventive therapy. For economic reasons, the French Headache Society is in favor of reimbursing these treatments for patients with severe migraine if at least two of the other reference treatments (beta-blockers, candesartan, amitriptyline, topiramate) are ineffective, intolerable or contraindicated.

2. Arrival of gepants on the French market

Rimegepant has proven its effectiveness in the treatment of migraine attacks [43]. It has also proved useful as a preventive treatment [44]. It has been approved by the EMA as both an attack treatment and a preventive treatment for patients with episodic migraine with at least four migraine attacks per month, and can therefore be prescribed for both indications. It has been available on the French market since October 2023, but is not reimbursed. The pharmaceutical company marketing rimegepant did not consult the Transparency Commission and chose to market this treatment without claiming reimbursement. It therefore has no SMR or ASMR at the time of writing this article.

Atogepant, has demonstrated its efficacy in the preventive treatment of episodic and chronic migraine [45,46]. It has also been shown to be effective in patients with episodic migraine for whom two to four classes of conventional oral preventive treatment have failed [47]. This treatment was approved in August 2023 by the EMA to prevent migraines in adults who

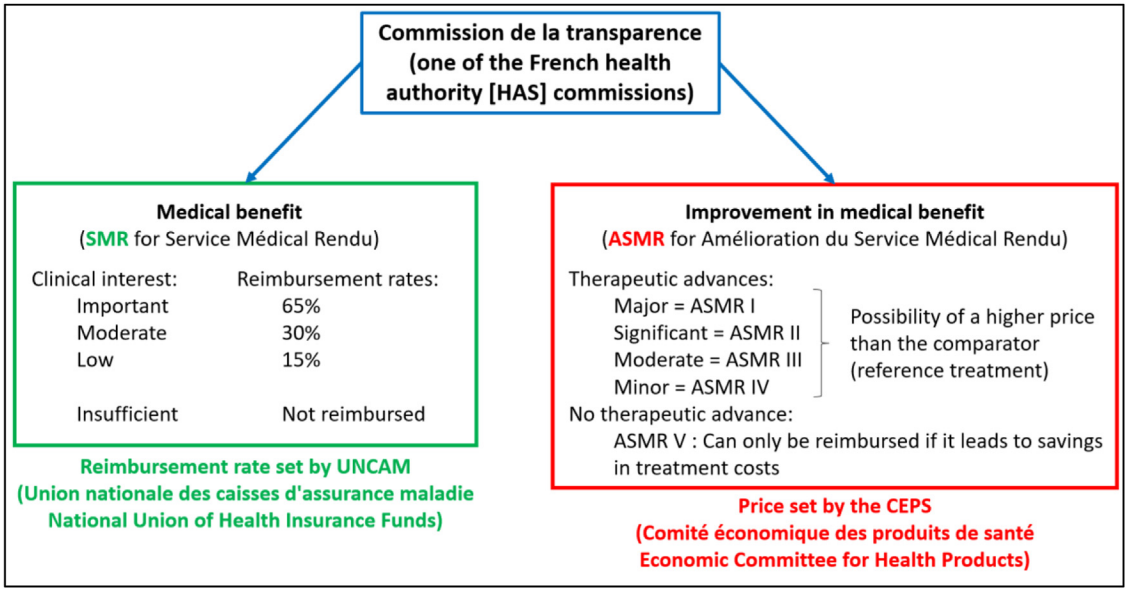

Fig. 1 – Simplified representation of the factors taken into account for a drug to be eligible for reimbursement and for a reimbursement price to be defined.

Table 2 – Opinions from the European and French authorities on the four monoclonal antibodies targeting the CGRP pathway and two gepants, and their availability on the French market.

	EMA approval	CT opinion	Approval for communities[b]	CEPS opinion	Availability on the French market
Eptinezumab (anti-CGRP)	MA 24/01/2022, Migraine prevention in adults who have migraines at least 4 days a month	05/10/2022 SMR important ASMR V[a]	Yes	Price negotiations fail, no reimbursement for patients	For hospital use only, available in certain healthcare facilities at no cost to the patient
Erenumab (anti-CGRP receptor)	MA 26/07/2018 Migraine prevention in adults who have migraines at least 4 days a month	27/02/2019 revised on 30/03/2022 SMR important ASMR V[a]	Yes		Not available
Fremanezumab (anti-CGRP)	MA 28/03/2019 Migraine prevention in adults who have migraines at least 4 days a month	16/09/2020 revised on 14/09/2022 SMR important ASMR V[a]	Yes		Available in pharmacies, not reimbursed, recommended retail price €270
Galcanezumab (anti-CGRP)	MA 14/11/2018 Migraine prevention in adults who have migraines at least 4 days a month	24/06/2020 SMR important ASMR V[a]	Yes		Available in pharmacies, not reimbursed, recommended retail price €245
Rimegepant	MA 24/02/2022 Acute treatment of migraine with or without aura in adults Migraine prevention in adults who have migraines at least 4 days a month	Not requested by the company	No	Not requested by the company	Available in pharmacies, not reimbursed; €60–80 for 2 tablets
Atogepant	MA 25/08/2023 Migraine prevention in adults who have migraines at least 4 days a month	06/12/2023 SMR important ASMR V[a]	Yes	Discussion in progress	Available in pharmacies, not reimbursed; €250–300 for 28 tablets

EMA: European Medicines Agency; CT: commission de la transparence of the French health authority (HAS); CEPS: Comité Économique des Produits de Santé (Economic Committee for Health Products); MA: marketing authorization.

[a] CT opinion for the four monoclonal antibodies: favourable opinion for reimbursement only as preventive treatment for migraine in patients with severe migraine with at least 8 migraine days per month, who have failed at least two preventive treatments and who have no cardiovascular problems.

[b] In order to be purchased and used in hospitals, medicines must be on the list of speciality medicines approved for use by local authorities and various public services.

have migraines at least four days a month. In December 2023, the HAS has come out in favour of possible reimbursement only for patients with at least eight migraine days per month and at least two failed prophylactic treatments (SMR important, ASMR V). It has been available in France since June 2024. Based solely on the efficacy and safety, atogepant can be offered as first-line treatment to all patients presenting with at least four migraine days per month, but the administrative rules in France for possible reimbursement are the same as those that apply to antibodies targeting the CGRP pathway.

Other gepants, including ubrogepant and zavegepant nasal spray, have proven effective as attack treatments [48,49]. These gepants were approved by the United States Food and Drug Administration (FDA) but not yet by the EMA. A recent study showed that taking ubrogepant very early on, from the prodrome phase, was effective in treating the attack [50]. What's more, the current data seem to be very favorable for gepants in terms of the risk of developing medication overuse headaches if taken repeatedly. That was shown in animals for olcegepant [51]. There are also human data with rimegepant and atogepant, which have been shown to be effective as prophylactic treatments and not to cause medication overuse headache. The half-life of these two drugs is around 11 hours. In the case of ubrogepant and zavegepant, the half-life is shorter (around six hours), which could theoretically modify the risk of headaches from overuse. However, the preclinical data for ubrogepant are entirely reassuring [52]. The gepants listed in this last paragraph are not currently available in France.

In conclusion, rimegepant (episodic migraine only) and atogepant are effective and well tolerated and should be offered to patients who need them. Taking into account only the EMA approval and the efficacy and safety data, it should be possible to offer these gepants as first-line treatment for all

patients who need preventive therapy (adults who have migraines at least four days a month) and rimegepant as an attack treatment. For economic reasons, the French Headache Society is in favor of reimbursing these treatments for patients with severe migraine if at least two of the other reference preventive treatments (beta-blockers, candesartan, amitriptyline, topiramate) are ineffective, intolerable or contraindicated. The French Headache Society also supports the reimbursement of rimegepant for the treatment of attacks in patients who have received failed regimens, have a contraindication to, or are intolerant to both nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans.

3. Update on the management of non-responders to triptans

Non-response to triptan has been defined recently and proposed criteria are presented in Table 3 [53]. However, it has been shown that some patients who do not respond to two triptans may respond well to a third or even a fourth triptan [54]. This study, using the German registry, showed that the highest response rates were seen with nasal and oral zolmitriptan, oral eletriptan and subcutaneous sumatriptan. Acute treatment optimization might include switching to one of the triptans with the highest response rates. Attack treatments are listed in Tables 4A and 4B with their usual doses, the main adverse effects and the main contraindications. Prophylactic treatments are listed in Tables 5A and 5B.

As proposed in the 2021 recommendations, another option for optimising attack treatment is to combine an NSAID and a triptan, if necessary with an anti-emetic (metoclopramide in particular). The use of a fixed combination of sumatriptan and naproxen has been shown to be superior to each of the compounds used in isolation, and deserves to be tried (not commercially available in France at time of writing) [55]. In fact, this fixed combination is the only one for which superiority over NSAIDs and triptan taken alone has been demonstrated in large randomized controlled trials. However, other combinations of NSAIDs and triptan may be of interest, and different combinations may be tried.

Another solution for optimizing attack treatment could be to change the therapeutic class and use a gepant. Rimegepant should be of interest to patients who do not respond optimally to triptans, or who have an adverse reaction or contraindication to both NSAIDs and triptans, especially as tolerance is excellent [56]. However, no studies performed specically on triptans/NSAIDs non-responders have been published. The results of the trial (NCT05509400) are eagerly awaited to see if they confirm this expectation.

Although there are no clearly defined criteria for declaring a patient resistant or refractory to an attack treatment with NSAIDs or gepant, it seems legitimate to try several molecules in the same class to optimize attack treatment.

Table 3 – Definition of resistant and refractory patients for triptans.

Triptans [53]	Responder when one or several triptans lead to effective acute treatment in at least three out of four migraine attacks Resistant in the presence of failure of at least 2 triptans Refractory in the presence of failure of at least 3 triptans, including subcutaneous sumatriptan 6 mg/0.5 mL

4. New data on the risk of certain pharmacological treatments during pregnancy

Topiramate is an effective treatment of episodic and chronic migraine. It is nevertheless important to note that recent meta-analyses clearly show that the effect in chronic migraine is less clear-cut than in episodic migraine and that treatments with monoclonal antibodies targeting the CGRP pathway or with botulinum toxin type A are more effective than topiramate in chronic migraine [19,57]. Real-world data on the use of botulinum toxin type A show good efficacy and safety [58]. Botulinum toxin type A can be used as a preventive treatment for chronic migraine, even in patients with a vascular contraindication to the use of CGRP-targeting treatments. There is insufficient data to support the use of botulinum toxin during pregnancy, although the data on exposure during the first trimester appear reassuring [59]. With regard to topiramate, recent data suggest that its use in pregnant women carries a risk of neurodevelopmental problems in the unborn child [60]. According to a large and well-conducted study, there is an increased risk of autism spectrum disorder, with a hazard ratio of 2.8 (95% CI: 1.4–5.7), as well as a risk of intellectual disability with a hazard ratio [95% CI] of 3.5 [1.4–8.6]. The effect size for this risk appears to be at least equivalent to that of valproate, whose risk is already well known. Consequently, the risks of neurodevelopmental disorders for an unborn child must be clearly explained to women of childbearing age. Following these data, the French national drug safety agency (Agence nationale de sécurité du médicament [ANSM]) has modified the conditions for prescribing and dispensing topiramate to girls, adolescents and women of childbearing age, with treatment initiation reserved for neurologists and an annual care agreement co-signed by the patient and the neurologist [61]. We therefore no longer recommend topiramate as first-line treatment in migraine for women of childbearing age. The same conditions have applied to valproate prescriptions since 2017. Thus, valproate is also not recommended for women of childbearing age if other therapeutic options are available.

It is important to note that all the data for valproate are consistent, with a constant excess risk in all the latest major studies, whether it is the risk of autism, intellectual disability or the development of psychiatric disorders [62,63]. It is not the case for topiramate. Indeed, the most recent study [62], which only looked at the risk of autism, found no association between in utero exposure to topiramate and the risk of developing an autism spectrum disorder at the age of 8. In fact, the association was substantially attenuated for topiramate after adjustment for indication and other confounders.

As a reminder, beta-blockers and amitriptyline can be used during pregnancy, although migraine attacks are usually rare. Both treatments have a high level of efficacy for episodic

Table 4A – Nonspecific acute migraine treatments.

	Dose, route	Main side effects	Main contraindications[a]
Analgesics (French Market Approval for the acute treatment of migraine, yes or no)			
Paracetamol (no)	500, 1000 mg (tablet) Maximum 4 g/day	Paracetamol: hepatic and hematologic toxicity	Severe hepatic insufficiency
Paracetamol + caffeine (no)	500 mg + 50 mg (tablet) Maximum 6 tablets/day	Caffeine: palpitation insomnia	
NSAIDs			
Diclofenac (no)	25, 50, 100 mg (tablet) Maximum 150 mg/day	Hemorrhagic syndrome Digestive disorder, dyspepsia, nausea, diarrhea, constipation Dizziness, asthenia	Active gastroduodenal ulcer Hypersensitivity to NSAIDs Hemorrhagic risk (cerebral, digestive other), Severe hepatic or renal insufficiency Pregnancy (after the 5th month)
Flurbiprofen (no)	8.75 mg (tablet) Maximum 5 tablets/day		
Ibuprofen (yes)	200, 400 mg (tablet) Maximum 1200 mg/day		
Indomethacin (no)	25, 75 mg (tablet) 100 mg (suppository) Maximum 300 mg/day		
Ketoprofen (yes)	100, 150 mg (tablet) 100 mg (suppository) Maximum 200 mg/day		
Naproxen (no)	550, 1000 mg (tablet) Maximum 1100 mg/day		
Acetylsalicylate acid, aspirin (no)	1000 mg (tablet, powder, disintegrating tablet) Maximum 3000 mg/day	Acetylsalicylate: digestive disorder hemorrhage, allergy, Reye syndrome	Acetylsalicylate: active gastroduodenal ulcer, hemorrhagic risk (cerebral, digestive other), pregnancy, asthma, severe hepatic, cardiac or renal insufficiency, hypersensitivity, pregnancy
Acetylsalicylate + metoclopramide (yes)	900 mg + 10 mg (powder) Maximum 3/day	Metoclopramide: dyskinetic syndrome, restlessness psychiatric disorder, endocrine disorder	Metoclopramide: gastrointestinal hemorrhage, digestive perforation, history of dyskinesia, extrapyramidal syndrome, children

[a] The contraindications and adverse reactions are not exhaustive, but are listed in order of frequency of occurrence. Interactions are not listed. See Vidal.

migraine [2]. In chronic migraine, the efficacy of propranolol has been considered fair [2], but a recent study showed that propranolol is as effective as topiramate in this indication [64]. Propranolol may therefore be a reasonable first-line option for patients with chronic migraine.

An alert published in August 2023 by the ANSM highlighted the potential risk for a child born to a father who had been exposed to valproate. In 2018, the EMA asked laboratories marketing valproate or its derivatives to conduct studies to better clarify the risks of these treatments. The results of one such study (EUPAS34201, presented in May 2023) suggested an increased risk of neurodevelopmental disorders in children whose epileptic fathers had been treated in the three months prior to conception with valproate or its derivatives. This risk ranged from 5.6% to 6.3% in children whose fathers had been exposed to valproate, versus 2.5% to 3.6% in those born to fathers treated with lamotrigine or levetiracetam [65]. It is therefore recommended from a legal point of view to inform men of this potential risk during the three months (spermatogenesis lasting an average of nine weeks) preceding

Table 4B – Specific acute migraine treatments.

	Dose (route)	Main side effects	Main contraindications[a]
Triptans (French Market Approval for the acute treatment of migraine, yes or no)			
Almotriptan (yes)	12.5 mg (tablet) Maximum 25 mg/day	Paresthesia of extremities, nausea, feeling of cold, dizziness, asthenia, ''chest syndrome'' (feeling of constriction in the chest and neck), flushing, somnolence Rare cases of coronary spasms, severe hypertension, serotonin syndrome	Coronary heart disease Wolff Parkinson White syndrome Myocardial infarction Peripheral arterial disease Raynaud TIA and stroke Uncontrolled hypertension Serious hepatic or renal insufficiency Concurrent treatment with a MAO inhibitor Cross allergy with sulfonamides (except for rizatriptan and zolmitriptan)
Eletriptan (yes)	20 or 40 mg (tablet) Maximum 80 mg/day		
Frovatriptan (yes)	2.5 mg (tablet) Maximum 5 mg/day		
Naratriptan (yes)	2.5 mg (tablet) Maximum 5 mg/day		
Rizatriptan (yes)	5, 10 mg (tablets), 10 mg (disintegrating tablet) Maximum 20 mg/day		
Sumatriptan (yes)	50 mg (tablets) Maximum 300 mg/day 10/20 mg (nasal spray) Maximum 40 mg/day 6 mg (subcutaneous injection) Maximum 12 mg/day		
Zolmitriptan (yes)	2.5 mg (tablet/disintegrating tablet) Maximum 10 mg/day Nasal spray 5 mg (not available in France)		
Gepants			
Rimegepant (yes, June 2023)	75 mg (tablet) Maximum 75 mg/day	Nausea Rare severe allergic reaction	History of hypersensitivity reaction to rimegepant
Ubrogepant (yes, January 2024)	50 mg, 100 mg (tablets) Maximum 200 mg/day	Nausea, drowsiness Rare severe allergic reaction	History of hypersensitivity reaction to Ubrogepant Concomitant use with a potent inhibitor of cytochrome P450 3A4 (CYP3A4)
Zavegepant (not available in France in 2024)	10 mg (nasal spray) Maximum 10 mg/day	Unusual taste, nausea, nasal discomfort, vomiting Rare severe allergic reaction	History of hypersensitivity reaction to zavegepant Severe (Child-Pugh class C) hepatic impairment Renal impairment (< 30 mL/min)
Ditans			
Lasmiditan (not available in France in 2024)	50 mg, 100 mg (tablets) Maximum 200 mg/day No more than one dose should be taken in 24 hours (FDA)	Common (> 2%): dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness. Significant driving impairment Central nervous system depression (dizziness, sedation) Rare (1%): hallucinations, euphoria Risk of misuse or abuse Rare cases of serotonin syndrome	Should be used with caution if used in combination with alcohol, cannabis or other CNS depressants No driving within the first 8 hours after intake (FDA)

[a] The contraindications and adverse reactions are not exhaustive, but are listed in order of frequency of occurrence. Interactions are not listed.

Table 5A – Oral prophylactic treatments: dosage, side effects and contraindications.

Treatment (French Market Approval, yes or no)	Daily dosage Minimum–maximum (mean daily dosage)	Main side effects	Main contraindications[a]
Amitriptyline (yes)	10–100 mg (25 mg) Once at dinner time	Dry mouth, somnolence, weight gain	Absolute: glaucoma, prostatic adenoma Relative: obesity
Beta-blocker			
Propranolol (yes)	20–240 mg (80 mg) BID or once in the morning (extended release)	Common: asthenia, poor tolerance to effort Rare: depression	Absolute: asthma, heart failure, atrio-ventricular block, bradycardia Relative: depression
Metoprolol (yes)	50–200 mg (100 mg) Once in the morning (extended release)		
Nebivolol (no)	5–10 mg (10 mg) Once in the morning		
Atenolol (no)	50–200 mg (100 mg) Once in the morning		
Timolol (no)	10–60 mg (20 mg) BID		
Candesartan (no)	8–32 mg (16 mg) BID or once a day	Hypotension	Absolute: heart failure, renal artery stenosis, renal impairment, pregnancy Relative: hypotension
Gepant			
Atogepant (yes)	60 mg, once a day	Constipation, nausea	Severe (Child-Pugh class C) hepatic impairment
Rimegepant (yes)	75 mg every other day	Nausea Rare severe allergic reaction	History of hypersensitivity reaction to rimegepant
Lisinopril (no)	5–40 mg (20 mg) Once a day	Hypotension, dry cough, exanthema, impaired renal function	Angio-edema, renal artery stenosis, renal impairment, hyperkaliemia, pregnancy
Lamotrigine (no)	25–300 mg (100 mg) Once or twice a day	Common: dizziness, insomnia Rare: serious hypersensitivity reactions, depression, suicidal ideation	Absolute: hypersensitivity to lamotrigine, breastfeeding Relative: previous allergy to another antiepileptic
Levetiracetam (no)	500–3000 mg Twice a day	Irritability, depression	Relative: renal impairment
Oxetorone (yes)	60–180 mg (120 mg) Once in the evening	Common: somnolence Rare: diarrhea, parkinsonism	Parkinson disease, parkinsonism, pregnancy
Pizotifene (yes)	50–300 mg (150 mg) BID	Common: sedation, weight gain	Obesity, glaucoma, prostatic adenoma, pregnancy
Topiramate (yes)	50–200 mg (100 mg) Once or twice a day	Common: paresthesia, weight loss, cognitive effects (word-finding difficulties), depression Rare: renal calculi, acute myopia with secondary angle closure glaucoma	Absolute: hypersensitivity to topiramate, pregnancy, glaucoma, severe pulmonary disease, metformin use, hepatic disease, nephrolithiasis, renal failure Do not use as first-line in women of childbearing age, annual care agreement if indication accepted Relative: depression, suicidal ideation
Valproate (no)	250–2000 mg (750 mg) Once in the evening or twice a day	Common: nausea, weight gain, somnolence, tremor, alopecia, augmentation des ASAT ALAT, hepatitis	Absolute: liver disease, pregnancy, mitochondrial disease Do not use in women of childbearing age, caution in male of childbearing potential (to be confirmed) Relative: obesity
Venlafaxine (no)	37.5–300 mg (75–150 mg) Once a day	Common: nausea, dry mouth, hyperhydrosis	Hypersensitivity to venlafaxine

[a] The contraindications and adverse reactions are not exhaustive, but are listed in order of frequency of occurrence. Interactions are not listed.

Table 5B – Injectable prophylactic treatments: dosage, side effects and contraindications.

Active component (French Market Approval, yes or no)	Daily dosage Minimum–maximum (mean daily dosage)	Side effects	Contraindications[a]
OnabotulinumtoxinA (yes)	31–39 injections (155–195 UI) in 7 muscular groups, quarterly	Injection site pain	Absolute: myasthenia gravis, amyotrophic lateral sclerosis
Anti-CGRP or CGRP receptor antibodies			
Erenumab (yes)	70–140 mg SC monthly	Injection site pain or redness, constipation, increase in blood pressure, allergy, alopecia, Raynaud phenomenon	Myocardial infarction, stroke, TIA, uncontrolled vascular risk factor Pregnancy
Eptinezumab (yes)	100–300 mg IV quarterly		
Fremanezumab (yes)	225 mg SC monthly 675 mg SC quarterly		
Galcanezumab (yes)	240 mg SC the first month, then 120 mg SC monthly		

[a] The contraindications and adverse reactions are not exhaustive, but are listed in order of frequency of occurrence. Interactions are not listed.

conception. However, the only study published so far is reassuring [66]. Further data is required to clarify this risk.

5. Marketing discontinuation of flunarizine from the French market

The Janssen-Cilag laboratory decided to stop marketing flunarizine at the end of October 2023. The withdrawal of this treatment from the market is therefore not a decision by the health authorities, but a commercial decision by the laboratory. This calcium antagonist also has anti-histaminic, anti-cholinergic and anti-dopaminergic effects. This treatment, which had proved its efficacy in several rather old randomized controlled trials [67], was approved in France as a second-line migraine treatment, providing relief for some patients. However, tolerance problems were not uncommon, and it was recommended not to use it for longer than six months. Thus, the level of recommendation was only moderate. Although other molecules are available for the preventive treatment of migraine, this withdrawal has a negative impact on the quality of life of some patients.

6. Conclusion

In conclusion, the four monoclonal antibodies targeting the CGRP pathway are effective and well tolerated and should be offered as preventative treatments to patients who need them. That is also the case for rimegepant (episodic migraine only) and atogepant. Taking into account only the EMA approval and the efficacy and safety data, it should be possible to offer these treatments targeting the CGRP pathways as first-line treatment for all patients who need preventive therapy. For economic reasons, the French Headache Society is in favor of reimbursing these treatments only for patients with severe migraine if at least two of the other reference preventive treatments (beta-blockers, candesartan, amitriptyline, topiramate) are ineffective, intolerable or contraindicated. So far, there is little evidence to rank CGRP mAbs, atogepant, and botulinum toxin in the treatment of chronic migraine. Gepants are well tolerated and may be useful as an acute treatment. For economic reasons, the French Headache Society also supports the reimbursement of rimegepant for the treatment of attacks in patients who have received a failed regimen, have a contraindication to, or are intolerant to both NSAIDs and triptans. Topiramate should not be used as first-line treatment in women of childbearing age (annual care agreement to be co-signed by the patient). This is obviously the case also for valproate in women, but recent data also show a potential risk in children born to fathers exposed within three months of conception.

Disclosure of interest

X. Moisset has received financial support from Allergan-Abbvie, Amgen-Horizon, Aptyspharma, Biogen, BMS, Dr Reddy's, Grünenthal, Lilly, Lundbeck, Teva, Merck-Serono, Novartis, Orion, Pfizer, Roche, Sanofi-Genzyme and Sun Pharma and non-financial support from SOS Oxygène not related to the submitted work. X. Moisset is associate editor of *Pain Reports* and of *Revue Neurologique*.

G. Demarquay has received financial support from Allergan-Abbvie, Lilly, Lundbeck, Novartis, Pfizer Teva not related to the submitted work.

S. de Gaalon has received financial support from Allergan-Abbvie, Bayer, Boerhinger, Lilly, Linde, Lundbeck, Novartis, Teva and BMS-Pfizer not related to the submitted work.

C. Roos has received financial support from Allergan-Abbvie, Biogen, Orkyn, Novartis, Mylan, Homeperf, Lilly, Teva, Ophtalmic, Lundbeck, Sanofi, Pfizer not related to the submitted work.

A. Donnet has received financial support from Abbvie/Allergan, Amgen, EliLilly, Lundbeck, Novartis, Perfood, Pfizer, and Teva not related to the submitted work.

P. Giraud has received financial support from Lundbeck, Merk, Pfizer and Sanofi.

E. Guégan-Massardier has received financial support from Allergan-Abbvie, Lundbeck, Novartis, Teva and BMS-Pfizer and Medtronic not related to the submitted work.

C. Lucas has received financial support from Abbvie, Homeperf, Grunenthal, EliLilly, Lundbeck, Orion, Pfizer, SOS Oxygène and Teva not related to the submitted work. C. Lucas is past-President of the SFEMC.

J. Mawet has received financial supports for boards, meeting presentations or travel expenses for congress from Lilly, Novartis, Abbvie, TEVA, Lundbeck, Pfizer, Orion Pharma, SOS Oxygen, Dr Reddy's and GEP Santé.

D. Valade and L. Grangeon declare that they have no competing interest.

V. Corand has received financial supports from Allergan-Abbvie, Lundbeck, Teva, BMS and Pfizer.

C. Gollion received direct honorarium for board membership and/or speak from Novartis, Teva, Lilly, Pfizer, Abbvie, Lundbeck and Orkyn, and grants from IHS and SFETD/APICIL for academic research, not related to the submitted work.

N. Moreau has received financial support from Grünenthal not related to the submitted work.

M. Lantéri-Minet has received financial support from Abbvie/Allergan, Amgen, Astellas, ATI, Boehringer, Boston Scientific, Glaxo-SmithKline, Grunenthal, EliLilly, Lundbeck, Medtronic, Menari, MSD, Novartis, Orion Pharma, Perfood, Pfizer, ReckittBenckiser, Saint-Jude, Sanofi-Aventis, Teva, UCB, UPSA and Zambon not related to the submitted work. M. Lantéri-Minet is associate editor of *Journal of Headache and Pain* and past-President of the SFEMC. The team of M. Lantéri-Minet in Nice Universitary Hospital/Côte Azur University (FHU InovPain) received academic support from PHRCn and PHRCir and grants from Eli Lilly, Lundbeck, Novartis, Pfizer, Teva.

A. Ducros received direct honorarium for board membership and/or speaking from Novartis, Lundbeck, Teva, Pfizer, Abbvie, Lilly, SOS oxygène. A. Ducros is associate editor of *Cephalalgia*, and past-President of the SFEMC. The team of AD in Montpellier University received academic support from PHRCn and PHRCir, and grants from Pfizer for academic research programs.

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