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ORIGINAL ARTICLE

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Level of therapeutic innovation from the registration studies of the new drugs for the prophylaxis of migraine

Domenico Motola PhD[1] | Greta Santi Laurini PharmD[1] | Giulia Bonaldo PharmD[1] | Nicola Montanaro PhD[2]

[1]Unit of Pharmacology, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

[2]Department of Pharmacology, Alma Mater Studiorum University di Bologna, Bologna, Italy

Correspondence
Domenico Motola, Unit of Pharmacology, Department of Medical and Surgical Sciences, University of Bologna, via Irnerio 48, 40126, Bologna, Italy.
Email: domenico.motola@unibo.it

Abstract

What is known and objective: Migraine is one of the most prevalent and disabling medical illnesses. Preventive drugs are used to reduce the frequency, severity, and duration of attacks. Most patients were no longer on their medication due to contra-indications or poor clinical response. Therefore, there is need for novel prophylactic agents for migraine. New preventive treatments are those of the class of calcitonin gene related peptide (CGRP)-targeting therapies. We aimed to assess the real level of therapeutic innovation of these new drugs.

Methods: The information on the new drugs was collected from several documents, including the European public assessment reports. The level of therapeutic innovation was assessed with the algorithm published by some of us in 2006.

Results: All new approved drugs (eptinezumab, galcanezumab, fremanezumab, erenumab) are indicated for the prophylaxis of migraine in adults who have at least four migraine days for month. All these drugs have been tested only in comparison to placebo. Their level of therapeutic innovation was only modest, that is, the lowest value of our algorithm.

Discussion: The new monoclonal antibodies of the class of CGRP targeting therapies have been authorized with efficacy data only against placebo. They do not offer additional clinical benefits compared to available therapies for the prevention of migraine attacks, with the exception of a lower frequency of administration and a more rapid effect. All this assigns to these drugs only a modest role in therapy according to our algorithm for therapeutic innovation with a significantly higher cost than similar therapies.

KEYWORDS
migraine, new drugs, therapeutic innovation

1 | WHAT IS KNOWN AND OBJECTIVE

Migraine is one of the most prevalent and disabling medical illnesses in the world. In GBD2015, migraine was ranked as the third most prevalent medical condition and the second most disabling neurological disorder worldwide in both males and females under the age of 50 years.[1,2] Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts.[3,4]

Three-quarters of patients with migraine are women.[5] The pharmacotherapy of migraine is classified into two types: acute treatments for relief of attacks when they occur and prophylactic treatments to reduce attack frequency and severity. Choice of acute treatment should include evaluations of efficacy, safety profile, contraindications, and cost. Triptans are the typical first-line treatment based on consolidated evidence for both effectiveness and safety. In patients not responsive to triptans, NSAIDs may be appropriate.[6] Other acute treatments for migraine, with varying level of supporting evidence are acetaminophen, dihydroergotamine, calcitonin gene-related peptide (CGRP) antagonists, and some nonpharmacologic treatments, all of these were associated with improved pain and function.[7] Preventive drugs are used to reduce the frequency, severity, and duration of attacks in patients with frequent migraine and also when acute medications are overused: among the others, beta-blockers (atenolol, propranolol), antidepressants (amitriptyline, nortriptyline, venlafaxine), topiramate, gabapentine and onabotulinumtoxin-A.[3] Hepp et al. have suggested that among patients with chronic migraine, up to 80% were no longer on their medication after 12 months and such discontinuation seems to be due to contraindications, or a history of poor clinical response or adverse effects. Therefore, and similarly to other chronic conditions, there is need for novel, more specifically target-oriented prophylactic agents for migraine.[8] A new preventive treatment option has been introduced recently with the class of CGRP-targeting therapies.

The novelty of the target (CGRP) and the topicality of the mechanism of action of these new monoclonal antibodies have promptly induced several authors and health stakeholders to claim this therapy as innovative. We aimed to assess the real level of therapeutic innovation of these new monoclonal antibodies for the prophylaxis of migraine by screening their registration studies with our already known algorithm.[9,10]

2 | METHODS

The information on the new drugs was collected from several documents, including the European public assessment reports (EPARs), which describe the steps, reasons, and commitments for the European approval of a given drug, and the summaries of product characteristics (SPC), the technical documents that list, among the others, therapeutic indications, dosages and adverse reactions for each drug and available scientific literature. The level of therapeutic innovation of new drugs was assessed with the algorithm published by us in 2005[9] and slightly modified in 2006.[10]

3 | RESULTS AND DISCUSSION

Table 1 lists the new monoclonal antibodies authorized by the European Medicine Agency (EMA) from 2018 to 2022. These drugs act by inhibiting the CGRP, thus preventing its binding to the corresponding receptor (eptinezumab,[11] galcanezumab,[12] fremanezumab[13] or directly blocking the CGRP receptor (erenumab[14]). As a consequence they prevent the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation, frequency and severity of migraine attacks. Galcanezumab, fremanezumab, and erenumab should be administered subcutaneously once monthly (in the case of fremanezumab also once every 3 months at the higher dose) while eptinezumab should be administered by intravenous infusion every 12 weeks. All drugs are indicated for the prophylaxis of migraine in adults who have at least four migraine days for month.

Table 2 lists the scores of the level of therapeutic innovation of the drugs under analysis based on the algorithm used.[10] The disease has been scored as serious since it is highly disabling. Migraine is a chronic neurological disease characterized by severe headache attacks with associated hypersensitivity to environmental stimuli. The disease is associated with higher frequencies of depression, anxiety disorders, sleep disturbances, cardiovascular risk, chronic pain syndromes, and suicide attempts. For availability of already existing treatment, these drugs received the score B, that is, drugs for a disease where subsets of patients are less responsive to marketed drugs and/or to other medical interventions. Finally, for the level of therapeutic effect, all drugs received the score C, that is, the score for minor or temporary benefit on some aspects of the disease. The combination of these scores produced a level of therapeutic innovation equal to "modest," that is, the lowest value of our algorithm.

On the basis of the data available to date, it can be stated that the new monoclonal antibodies for the prevention of migraine in adults represent only a modest therapeutic innovation, whose only advantage over established therapies is represented by the lower frequency of administration and the faster onset of the effect. All these new drugs have been tested only in comparison to placebo, although the EMA guidelines recommend that drugs for prophylaxis should be tested also with an active comparator.[15] The use of an active comparator is recommended also for internal validation because of the large and highly variable placebo effect in prophylactic migraine studies. In the corresponding EPARs, justifications are given for the non-use of the active comparator, stating for example that the well-known side effects of the established migraine prophylactic treatments may unblind the patients, or the difference in administration routes (oral for beta-blockers and topiramate, SC once monthly for erenumab) may hamper the design of a double-blinded study.[14] However, at least in the latter case, a double-dummy design could have overcome such obstacle.

As regards the extent of the therapeutic effect, this has to be considered modest in terms of reduction of monthly migraine days (primary end point). This low level of therapeutic efficacy is also recognized in the assessment reports of the drugs analysed. This efficacy was measured against placebo, so it is conceivable that a comparison with an active comparator could have given similar or even worse results.

Moreover, these drugs are very expensive, much more expensive than the drugs traditionally used for this purpose, and their cost for health services is even higher since, in at least one case, intravenous administration (eptinezumab) requires to resort to health centre.

TABLE 1 Calcitonin gene related peptide (CGRP) targeting therapies approved by the EMA

Active substance/ trade name	Approved therapeutic indications	Authorization date	Mechanism of action	Route of administration and posology
Erenumab/ Aimovig	AIMOVIG is indicated for prophylaxis of migraine in adults who have at least four migraine days per month.	26/07/2018	Fully human monoclonal immunoglobulin G2 that is directed against the calcitonin gene-related peptide (CGRP) receptor complex and inhibits the action of CGRP.	SC/The recommended dose is 70 mg erenumab every 4 weeks
Galcanezumab/ Emgality	EMGALITY is indicated for the prophylaxis of migraine in adults who have at least four migraine days per month.	14/11/2018	Galcanezumab is a humanized monoclonal antibody of IgG4 that binds calcitonin gene-related peptide (CGRP) thus preventing its biological activity. Elevated blood concentrations of CGRP have been associated with migraine.	SC/The recommended dose is 120 mg galcanezumab injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
Fremanezumab/ Ajovy	AJOVY is indicated for prophylaxis of migraine in adults who have at least four migraine days per month.	28/03/2019	Fremanezumab is a fully humanized immunoglobulin G2 (IgG2) monoclonal antibody derived from a murine precursor. Fremanezumab is a potent, selective calcitonin gene-related peptide (CGRP) mAb that binds to and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor.	SC/Two dosing options are available: 225 mg once monthly (monthly dosing) or 675 mg every 3 months (quarterly dosing)
Eptinezumab/ Vyepti	VYEPTI is indicated for the prophylaxis of migraine in adults who have at least four migraine days per month.	24/01/2022	Recombinant humanized anti-CGRP (calcitonin gene-related peptide) monoclonal IgG1 antibody. Eptinezumab binds to α- and β-forms of human CGRP ligand. This translates into fast blockage of the pharmacological effects of circulating CGRP in humans. As a result, eptinezumab prevents the activation of the CGRP receptors and hence the downstream cascade of physiological events linked to initiation, frequency and severity of migraine attacks.	IV/100 mg by intravenous infusion every 12 weeks

Abbreviation: EMA, European Medicine Agency.

According to Hwang et al.,[16] in several European and non-European Countries, the therapeutic indication of these drugs has been narrowed and a request of a substantial price reductions (from 23% to 46%) has been recommended for the new therapies to be cost-effective for the intended patient population. In Italy, country not covered by the study by Hwang et al., three monoclonal antibodies have been admitted to reimbursement with ex-factory prices between 425 € (minus a negotiated, but not made public, discount the national health service structures) for one prefilled syringe of erenumab or galcanezumab[17,18] to 470 € for one pre filled syringe of fremanezumab.[19] By comparison, the cost of 1 month of preventive therapy with oral topiramate, considering a daily dose of 100 mg and the corresponding ex-factory price of the medicinal product, would be 41.46 Euros.

The absence of additional therapeutic benefits for the prevention of migraine attacks for these new drugs has also been confirmed by other regulatory agencies such as the French one (no added benefit) and the German one (additional benefit not demonstrated except in patients not responsive or not tolerant to other therapies).[16]

Moreover, as with any new drug, even with a new mechanism of action, it is not currently possible to know the real safety profile of these drugs.

TABLE 2 Scores for the assessing the level of therapeutic innovation

Active substance/ trade name	Approved therapeutic indications	Disease seriousness	Comment	Availability of treatments	Comment	Therapeutic effect	Comment	Level of therapeutic innovation
Erenumab/Aimovig	Aimovig is indicated for prophylaxis of migraine in adults who have at least four migraine days per month.	A (Serious)	The disease is serious since it is highly disabling. Migraine is a chronic neurological disease characterized by severe headache attacks with associated hypersensitivity to environmental stimuli The disease is associated with higher frequencies of depression, anxiety disorders, sleep disturbances, cardiovascular risk, chronic pain syndromes, and suicide attempts.	B (Drug for a disease where subsets of patients are less responsive to marketed drugs and/or other medical interventions)	The standard of care in migraine prophylaxis is quite heterogeneous. Existing treatments are frequently associated with variable efficacy and poor safety and tolerability, leading to low persistence and adherence rates	C (Minor or temporary benefit on some aspects of the disease)	Phase 2/3, multicentre, double-blind, randomized, placebo-controlled, study to evaluate the efficacy and safety of two doses of SC Aimovig every 4 weeks for 12 weeks in subjects with chronic migraine (≥8 monthly migraine days, ≥15 monthly headache days at baseline). Six hundred and sixty-seven patients were randomized (3:2:2) to receive placebo, Aimovig 70 mg and Aimovig 140 mg. Both dosages reduced the number of monthly migraine days (primary endpoint) from a baseline mean of around 18 days by 6.64 and 6.63 days, respectively, compared to a reduction in the placebo group of 4.18 days, resulting in a difference in LSM of −2.46 and −2.45, respectively, and p values of <0.001. Phase 3, multicentre, double-blind, randomized, placebo-controlled, study to evaluate the efficacy and safety of two doses of SC Aimovig every 4 weeks for 24 weeks in subjects with episodic migraine (≥4 and <15 migraine days per month with <15 headache days per month at baseline). Nine hundred and fifty-five patients	C (Modest)

(Continues)

TABLE 2 (Continued)

Active substance/ trade name	Approved therapeutic indications	Disease seriousness	Comment	Availability of treatments	Comment	Therapeutic effect	Comment	Level of therapeutic innovation
							were randomized (1:1:1) to receive placebo, Aimovig 70 mg and Aimovig 140 mg. Aimovig at 70 and 140 mg reduced the number of monthly migraine days (primary endpoint) from a baseline mean of around 8 days by 3.23 (3.58, 2.88) and 3.67 (4.02, 3.33) days, respectively, compared to a reduction in the placebo group of 1.83 (2.18, 1.48) days, resulting in a difference in LSM of −1.40 and −1.85, respectively, and *p* values of <0.001.	
Eptinezumab/ Vyepti	VYEPTI is indicated for the prophylaxis of migraine in adults who have at least four migraine days per month.	A (Serious)	Idem (See above)	B (Drug for a disease where subsets of patients are less responsive to marketed drugs and/or other medical interventions)	Idem (See above)	C (Minor or temporary benefit on some aspects of the disease)	The two pivotal Phase 3 efficacy studies were both randomized, double-blind, placebo-controlled studies. Study ALD403-CLIN-006 included patients with frequent episodic migraine, defined as 4–14 Monthly headhache days (MHDs)/ month at baseline. Study ALD403-CLIN-011 included patients with chronic migraine, defined as ≥15 to ≤26 headache days of which at least 8 with features of migraine. Overall, a modest but consistent treatment effect in terms of reduction of migraine headache days, migraine responder rates, percentage of subjects	C

TABLE 2 (Continued)

Active substance/ trade name	Approved therapeutic indications	Disease seriousness	Comment	Availability of treatments	Comment	Therapeutic effect	Comment	Level of therapeutic innovation
							with a migraine on the day after dosing, change in migraine medication days, and supportive endpoints was found for all eptinezumab treatment arms. The superiority of the 300 and 100 mg group versus placebo was found to be consistently statistically significant. Although the difference on the primary efficacy endpoint was found to be rather modest, the size of treatment effect is in a range comparable to other anti-CGRP therapies recently authorized for the prevention of migraine in adults. Superiority of eptinezumab compared to placebo in reducing the frequency of migraine days, as well in decreasing the burden of migraine episodes and symptoms in patients with episodic and chronic migraine is considered demonstrated. The difference from placebo in mean reduction of migraine days was rather modest.	
Galcanezumab/ Emgality	EMGALITY is indicated for the prophylaxis of migraine in adults who have at least four migraine days per month.	A (Serious)	Idem (See above)	B (Drug for a disease where subsets of patients are less responsive to marketed drugs and/or other medical interventions)	Idem (See above)	C (Minor or temporary benefit on some aspects of the disease)	Three randomized, double-blind, placebo-controlled studies in CM (chronic migraine) and EM (episodic migraine) provide efficacy and safety data of galcanezumab in the prophylaxis of migraine in adults.	C

(Continues)

TABLE 2 (Continued)

Active substance/ trade name	Approved therapeutic indications	Disease seriousness	Comment	Availability of treatments	Comment	Therapeutic effect	Comment	Level of therapeutic innovation
							Study CGAG and Study CGAH are pivotal for EM and Study CGAI is pivotal for CM. They all include the proposed registration dose of 120 mg, with a loading dose of 240 mg, as well as the 240 mg dose regimen. Studies CGAG and CGAH are phase 3, randomized, double-blind, placebo-controlled to evaluate the effect of galcanezumab compared to placebo on the overall change from baseline in mean monthly migraine days in subjects with episodic migraine. Study CGAI is a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of galcanezumab through the overall mean change from baseline in mean monthly migraine headache days as prevention of chronic migraine. In all three studies, the magnitude of treatment effect seems limited; however, it is acknowledged that there is no agreed minimal clinically relevant effect in terms of decrease in MHD in the literature or in the clinical practice. The applicant has provided tabulated indirect comparison data with	

TABLE 2 (Continued)

Active substance/ trade name	Approved therapeutic indications	Disease seriousness	Comment	Availability of treatments	Comment	Therapeutic effect	Comment	Level of therapeutic innovation
							available treatments in order to contextualize treatment benefit. Overall, galcanezumab treatment effect seems comparable with that of historical data from topiramate and Botox published studies. However, although the applicant's efforts are appreciated, the indirect comparison is not supported by a sound methodology, and its usefulness for the evaluation of treatment benefit is limited.	
Fremanezumab/ Ajovy	AJOVY is indicated for prophylaxis of migraine in adults who have at least four migraine days per month.	A (Serious)	Idem (See above)	B (Drug for a disease where subsets of patients are less responsive to marketed drugs and/or other medical interventions)	Idem (See above)	C (Minor or temporary benefit on some aspects of the disease)	The primary evaluation of efficacy was based on the data from two nearly identical Phase 3, 16-week, multicentre, double-blind, placebo-controlled, randomized, parallel-group studies (Study 30049 in patients with CM and Study 30050 in patients with EM), which tested the proposed dose regimen of 225 mg monthly or 675 mg every 3 months (quarterly). The applicant demonstrated superiority of fremanezumab versus placebo in the reduction in the monthly average number of headache days of at least moderate severity (primary endpoint in study 30049), and in the monthly average number of migraine days (primary	C

(Continues)

TABLE 2 (Continued)

Active substance/ trade name	Approved therapeutic indications	Disease seriousness	Comment	Availability of treatments	Comment	Therapeutic effect	Comment	Level of therapeutic innovation
							endpoint in study 30050). Key secondary endpoints have also been met, indicating the potential of fremanezumab to decrease the number, duration and burden of migraine symptoms. However, albeit demonstration of the statistical significance of the treatment effect, the absolute difference compared to placebo-control was relatively small due to a significant placebo effect. Especially in the treatment of EM the difference in treatment effect was small. This may limit the usefulness of fremanezumab in this group of patients and should be considered with regard to the benefit–risk-evaluation. Reduction of acute medications could be considered a clinical relevant additional benefit, but even for this endpoint the absolute difference to placebo was rather small.	

Note: Algorithm used to assign the overall score for innovation. Disease seriousness: A, drugs for serious diseases; B, drugs for risk factors for serious diseases; C, drugs for nonserious diseases. Availability of treatments: A, drugs for diseases without recognized standard treatment; B, drugs for diseases where subsets of patients are less responsive to marketed drugs and/or other medical interventions; C, drugs for diseases responsive to marketed drugs or other medical interventions (C 1, more effective or safer or with a better kinetics than existing drugs; C 2, mere pharmacological innovation, i.e., drugs with a new mechanism of action; C 3, mere technological innovation, i.e., a new chemical or biotechnological product with a therapeutic role similar to already existing ones). Therapeutic effect: A, major benefit on clinical end-points (e.g., increased survival rate and/or quality of life) or validated surrogate endpoints; B, partial benefit on the disease (on clinical or validated surrogate end-points) or limited evidence of a major benefit (inconsistent results); C, minor or temporary benefit on some aspects of the disease (e.g., only partial symptomatic relief of a serious disease).[9]

4 | WHAT IS NEW AND CONCLUSION

In conclusion, the new monoclonal antibodies of the class of CGRP targeting therapies have been authorized with efficacy data only against placebo (disregarding the recommendations of the specific EMA guidelines). They do not offer additional clinical benefits compared to available therapies for the prevention of migraine attacks, with the exception of a lower frequency of administration and a more rapid effect, and with a safety profile to be defined. All this assigns to these drugs only a modest role in therapy according to our algorithm for therapeutic innovation[9] with a significantly higher cost than similar therapies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Domenico Motola https://orcid.org/0000-0001-6253-4014
Giulia Bonaldo https://orcid.org/0000-0002-3302-1460
Nicola Montanaro https://orcid.org/0000-0002-5710-8077

REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545-1602.
2. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16:877-897.
3. Dodick DW. Migraine. *Lancet*. 2018;391:1315-1330.
4. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1603-1658.
5. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(10268):51-60. doi:10.1016/S0140-6736(20)32544-7
6. Burch R, Rayhill M. Acute treatment for migraine: contemporary treatments and future directions. *JAMA*. 2021;325(23):2346-2347. doi:10.1001/jama.2021.7275
7. VanderPluym JH, Halker Singh RB, Urtecho M, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. *JAMA*. 2021;325(23):2357-2369. doi:10.1001/jama.2021.7939
8. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia*. 2015;35(6):478-488. doi:10.1177/0333102414547138
9. Motola D, De Ponti F, Rossi P, Martini N, Montanaro N. Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003. *Br J Clin Pharmacol*. 2005;59(4):475-478. doi:10.1111/j.1365-2125.2004.02320.x
10. Motola D, De Ponti F, Poluzzi E, et al. An update on the first decade of the European centralized procedure: how many innovative drugs? *Br J Clin Pharmacol*. 2006;62(5):610-616. doi:10.1111/j.1365-2125.2006.02700.x
11. European Medicines Agency. *European Public Assessment report*, Vyepti. EMA/9446/2022. Accessed April 28, 2022. https://www.ema.europa.eu/en/documents/assessment-report/vyepti-epar-public-assessment-report_en.pdf.
12. European Medicines Agency. *European Public Assessment report*, Emgality. EMA/708631/2018. Accessed April 28, 2022. https://www.ema.europa.eu/en/documents/assessment-report/emgality-epar-public-assessment-report_en.pdf.
13. European Medicines Agency. *European Public Assessment report*, Ajovy. EMA/118499/2019. Accessed April 28, 2022. https://www.ema.europa.eu/en/documents/assessment-report/ajovy-epar-public-assessment-report_en.pdf.
14. European Medicines Agency. *European Public Assessment report*, Aimovig. EMA/CHMP/413393/2018. Accessed April 28, 2022. https://www.ema.europa.eu/en/documents/assessment-report/aimovig-epar-public-assessment-report_en.pdf.
15. European Medicines Agency. *Guideline on clinical investigation of medicinal products for the treatment of migraine*. CPMP/EWP/788/01 Rev. 1. Accessed April 28, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-migraine_en.pdf.
16. Hwang TJ, Vokinger KN, Kesselheim AS. New treatments for migraine-therapeutic ratings and comparative coverage in the US, Canada, and Europe. *JAMA Intern Med*. 2022;182(2):101-102. doi:10.1001/jamainternmed.2021.7168
17. Agenzia italiana del Farmaco. Determination July 10, 2020. Accessed April 28, 2022. https://www.aifa.gov.it/documents/20142/847786/Determina_DG-727-2020_Aimovig.pdf.
18. Agenzia italiana del Farmaco. Determination July 10, 2020. A/RRI. Accessed April 28, 2022. https://www.aifa.gov.it/documents/20142/847786/Determina_DG-732-2020_Emgality.pdf.
19. Agenzia italiana del Farmaco. Determination July 10, 2020. Accessed April 28, 2022. https://www.aifa.gov.it/documents/20142/847786/Determina_DG-730-2020_Ajovy.pdf.

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