

Gabapentin

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande. La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 2. Medicines for pain and palliative care > 2.1. Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)

Codes ATC: N02BF01

Indication	Neuropathic pain Code ICD11: 8E43.0Z
INN	Gabapentin
Type de médicament	Chemical agent
Type de liste	Liste de base
Formulations	Oral > Solid: 100 mg ; 200 mg ; 300 mg ; 400 mg ; 600 mg ; 800 mg
Historique des statuts LME	Demande refusée en 2017 (TRS 1006)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets .
Wikipédia	Gabapentin
DrugBank	Gabapentin

Recommandation du comité d'experts

The Expert Committee considered the uncertainty in efficacy estimates as a result of publication and outcome reporting biases in the currently available evidence for gabapentin. The Committee did not recommend inclusion of gabapentin on the EML for neuropathic pain because of its uncertain benefits.

Contexte

The application proposed the addition of gabapentin to the core list of the EML as an analgesic agent for the management of neuropathic pain (central and peripheral) in adults. In 2017 the Expert Committee examined four medicines for pain and palliative care for the first time: methadone, fentanyl, tramadol and gabapentin.

Pertinence pour la santé publique

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" (1, 2). It is commonly associated with back pain (e.g. lumbar or cervical radiculopathy), diabetes (painful diabetic neuropathy), post-surgical pain, HIV-AIDS, and herpes zoster (post-herpetic neuralgia) but can also arise through many other diseases or injuries. Specific clinical features include symptoms such as paraesthesia, burning or shooting pains, altered sensation (numbness, allodynia or hyperalgesia) and locally altered autonomic function (3). In the absence of both a "gold standard" for defining cases and a clinical code for routine health-care use, it is impossible to identify the precise prevalence of neuropathic pain, for example through the 2013 Global Burden of Disease study (4). The application provided estimates of prevalence based on specific causes of neuropathic pain (e.g. diabetes) or on self-reports of some symptoms, assuming prevalence in the overall population of the order of 7–10% (5).

The estimates provided appear to substantially overestimate the burden of disease. Few studies evaluated the incidence through appropriate methods, particularly use of a standard process to confirm diagnosed cases in general populations. In two European studies (6, 7), the incidence per 10 000 person-years was 3.0 (95% confidence interval (CI) 3.0–3.1) and 4.2 (95% CI 3.8–4.5) for post-herpetic neuralgia, 2.8 (95% CI 2.7– 2.8) and 7.2 (95% CI 6.7–7.7) for painful diabetic neuropathy, and 0.11 (95% CI 0.09–0.12) and 0.22 (95% CI 0.15–0.33) for phantom limb pain. These estimates differ considerably from those provided in the application and seem to be more reliable. The incidence of these three conditions increased with age. Neuropathic pain has a significant adverse impact on all measured aspects of life, health and function (8), irrespective of the underlying diagnosis (9).

Bénéfices

The application included data on the following medicines: tricyclic antidepressants (TCAs; amitriptyline), serotonin–norepinephrine re-uptake inhibitors (SNRIs; mainly duloxetine), pregabalin and gabapentin. All were considered to be first-line options for neuropathic pain, but amitriptyline is the only one currently included in the EML. The evidence supporting the application was based on a recent systematic review, metaanalysis and GRADE-based recommendations (10). The review searched for full reports of randomized, controlled, double-blind studies published in peer-reviewed journals between 1966 and 2014 and for unpublished trials. A supplementary search of PubMed was conducted on 26 February 2016 to update the application results. The population included in the trials comprised patients of any age with neuropathic pain according to the IASP definition (i.e. pain caused by a lesion or disease of the somatosensory nervous system) (2). The interventions considered were systemic or topical treatments (oral, sublingual, oropharyngeal, intranasal, topical, subcutaneous, intradermal, and smoking) lasting at least 3 weeks. Single-administration treatments with long-term efficacy (high concentration capsaicin 8% patches, botulinum toxin) were included if there was a minimum follow-up of 3 weeks. Studies in which intramuscular, intravenous or neuraxial routes of administration were used and those of pre-emptive analgesia were excluded. Randomized, double-blind, placebo-controlled studies with parallel group or crossover study designs were included; studies in which the primary outcome measure was not pain were excluded. Quality was assessed using the five-point Oxford Quality Scale (11). Additional dimensions assessed for risk of bias were: allocation concealment, incomplete accounting of outcome events, selective outcome reporting, stopping early for benefit, use of invalidated outcome measures, carry-over effects in crossover trials, and inadequate sample size. A total of 229 reports, across a number of agents, were included in the published meta-analysis (10); 127 (55%) of the 229 trials were in patients with diabetic painful polyneuropathy or post-herpetic neuralgia. The mean Oxford Quality Scale score was 4.1 (SD 0.87; range 2–5). Studies were associated with potential or established major shortcomings in several areas – incomplete outcome data, size, duration and outcome reported. The application identified publication bias through funnel plots and Egger regression as a potential distortion of the results. It used the “trim and fill” method to correct for funnel plot asymmetry arising from publication bias; this method suggested 34 theoretically missing studies. The overall effect size of benefit was reduced from an odds ratio (OR) of 1.8 (95% CI 1.7–1.9) to OR 1.6 (95% CI 1.5–1.7). This suggests about a 25% overstatement of treatment effects on pain reduction. The correction was applied to all studies, irrespective of individual medicines. It is possible that the correction of benefit associated with studies evaluating gabapentin is different from that of studies evaluating the other pharmacotherapies. Furthermore, susceptibility-to-bias analyses, another approach used to deal with publication bias, assume that results in published studies are unbiased, which is not the case. With regard to risk of bias and publication bias, the application overlooked data (see “Additional evidence” section below), while heterogeneity was not presented. The number needed to treat (NNT) to achieve 50% pain relief non-attributable to placebo for the evaluated medications ranged between 4 and 9: amitriptyline 4.3 (95% CI 3.6–5.3), gabapentin 6.3 (95% CI 5.0–8.3), pregabalin 8.8 (95% CI 7.5–10.8), SNRIs 6.4 (95% CI 5.2– 8.4). In total, the assessment was based on 14 randomized controlled trials of gabapentin (900–3600 mg/day). The trials were conducted predominantly in patients with postherpetic neuralgia, painful polyneuropathy (mainly diabetic), spinal cord injury, post-amputation pain and peripheral nerve injury. The combined NNT for gabapentin across the 14 studies was 6.3 (95% CI 5.0–8.3), and there was no evidence of a dose–response effect. The application also provided data on head-to-head trials of gabapentin and TCAs, showing conflicting results. One trial reported that gabapentin had lower efficacy than amitriptyline in the management of neuropathic pain resulting from spinal cord injury (12), while two others reported no difference in treatment efficacy between gabapentin and nortriptyline or amitriptyline (13, 14). The application also mentioned a Cochrane systematic review (15) that partitioned the analysis according to pain etiology and considered the overall evidence for benefits and harms at some risk of bias. Data were largely concordant: gabapentin was considered effective in post-herpetic neuralgia (NNT 8.0; 95% CI 6.0–12) and painful diabetic neuropathy (NNT 5.9; 95% CI 4.6–8.3). The authors concluded that there were insufficient data in other pain conditions, including fibromyalgia, to allow any reliable conclusion to be reached.

Torts

Analysis of adverse effects in trials of gabapentin for neuropathic pain was based on a meta-analysis of 11 studies (10); the combined number needed to harm (NNH) was 25.6 (95% CI 15.3–78.6). The NNH was calculated as the number of patients who needed to be treated for one patient to drop out because of adverse effects. When specific adverse events were examined, dizziness, somnolence (or drowsiness or sedation) and, in a few studies, peripheral oedema and confusion had a prevalence of >10%, higher than in the placebo group. The NNH for dizziness was 5.1 (95% CI 4.3–6.3) and for somnolence 7.1 (95% CI 5.7–9.4). In the Cochrane review of gabapentin in fibromyalgia and neuropathic pain (15), 62% of gabapentin-treated patients and 50% of those given placebo experienced at least one adverse event in 17 studies with 4002 participants. The risk ratio (RR) for adverse events was 1.25 (95% CI 1.2–1.3) and the NNH was 8.6 (95% CI 6.8–12). Serious adverse events were no more common for gabapentin than for placebo (RR 1.2; 95% CI 0.8–1.7). The NNH for somnolence, drowsiness or sedation was 11 (95% CI 9.4–14; 4125 participants), for dizziness 7.6 (95% CI 6.6–8.8; 4125 participants) and for peripheral oedema 21 (95% CI 16–30; 3220 participants). Gabapentin was associated with an increased risk of ataxia or gait disturbance with an NNH of 13 (95% CI 9–24; 544 participants) (15).

Preuves supplémentaires

In 1993, gabapentin (Neurontin®, Pfizer) was first approved by the U.S. Food & Drug Administration (FDA) as an adjunctive therapy for epilepsy. In 2002, the drug was approved for the management of post-herpetic neuralgia, its only pain-related indication. Parke-Davis and Pfizer, the companies responsible for promoting and marketing gabapentin, adopted a publication strategy “to disseminate the information as widely as possible through the world’s medical literature” (16). This promotion was judged to be illegal and fraudulent: in 2004, American pharmaceutical manufacturer Warner-Lambert pleaded guilty and agreed to pay more than US\$ 430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division’s marketing scheme of unapproved uses of gabapentin (17). This was one of the largest settlements reached between the United States Department of Justice and pharmaceutical companies. Following litigation, internal company documents relating to gabapentin publication strategy have been made publicly available through two separate legal actions (18, 19). These sources were analysed in a series of studies (20–23) that documented publication and outcome reporting biases and data manipulation. The magnitude of these biases is highly relevant, and affects the evidence presented in the application. Firstly, in 2009, of 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis, eight were never published. Secondly, there were irreconcilable differences between the original protocols, statistical analysis plans, interim research reports and the main publications relating to most trials. For eight of the 12 published trials, the primary outcome defined in the published report differed from that described in the protocol. In three out of 10 trials, the numbers of participants randomized and analysed for the primary outcome and the type of analysis for efficacy and safety in the internal research report and the trial publication differed. Different subsets of participants were included in the analysis, leading to different findings: in one trial, the main findings in the publication did not include data from 40% of participants actually randomized. These changes are likely to have unbalanced the comparisons, favouring responsive patients and excluding poor responders in the arms allocated to gabapentin, thereby inflating the size of the effect attributable to the drug. The important differences between the internal and published documents about the number of patients or the plans of the analyses invalidate the study design (i.e. downgrading the evidence from experimental to observational), as the randomization is no longer valid.

Rapport coût/efficacité

Comparative pricing data were obtained from the MSH (Management Sciences for Health) International Medical Products Price Guide (26). Prices based on the defined daily dose (DDD) of gabapentin varied from US\$ 0.36 to US\$ 2.31; prices of amitriptyline varied from US\$ 0.04 to US\$ 0.34. Analysis of comparative pricing for gabapentin was limited by the absence of price data from suppliers, and price data were available from only one buyer source each for the 100- mg and 400-mg doses of gabapentin and three for the 300-mg dose. Cost–utility analysis NICE recently completed a cost–utility analysis across treatments typically recommended as first-line for neuropathic pain (24). Medicine prices were taken from the March 2013 Electronic Drug Tariff register of the United Kingdom National Health Service, and health benefit was valued in quality-adjusted life-years (QALYs). All medicines were associated with positive incremental net monetary benefits, assuming a QALY value of £20 000 and £30 000. Based on the outcome of the cost–utility analysis, the NICE Guideline Development Group recommended gabapentin and

amitriptyline as initial treatment options for neuropathic pain.

Directives de l'OMS

Currently there are no WHO guidelines for the treatment of neuropathic pain. Guidelines from the IASP Special Interest Group on Neuropathic Pain (NeuPSIG) (10), the United Kingdom National Institute for Health and Care Excellence (NICE) (24) and the European Federation of Neurological Societies (25) report that TCAs, $\alpha 2\delta$ calcium channel ligands (gabapentin and pregabalin), and selective SNRIs should be considered as first-line therapy, with the choice of medicine being guided by clinical and therapeutic factors (e.g. contraindications, interactions), and by medicine availability and affordability

Disponibilité

Gabapentin has regulatory approval as a prescription-only medicine from: FDA, European Medicines Agency (EMA), Australian Therapeutic Goods Administration (TGA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada. However, FDA indication is limited to post-herpetic neuralgia, and PMDA and Health Canada indicate gabapentin only for the treatment of epilepsy. Regulatory approval of gabapentin for neuropathic pain: FDA, USA: Post-herpetic neuralgia EMA, European Union: Neuropathic pain TGA, Australia: Neuropathic pain PMDA, Japan: Not approved for neuropathic pain Health Canada: Not approved for neuropathic pain

Autres considérations

The Committee acknowledged the importance of the issues of publication and outcome reporting bias.

1. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630–5.
2. Jensen TS, Baron R, Haanpaa M, Kalso E, Loeser JD, Rice AS et al. A new definition of neuropathic pain. *Pain*. 2011;152(10):2204–5.
3. McMahon S, Koltzenburg M, Tracey I, Turk D, editors. *Wall and Melzack's textbook of pain*, sixth edition. Philadelphia: Saunders; 2013.
4. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743–800.
5. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain*. 2014;155(4):654–62.
6. Hall GC, Morant SV, Carroll D, Gabriel ZL, McQuay HJ. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. *BMC Fam Pract*. 2013;14:28.
7. Dieleman JP, Kerklaan J, Huygen FJ, Bouma PA, Sturkenboom MC. Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain*. 2008;137(3):681–8.
8. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. *J Pain*. 2006;7(4):281–9.
9. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. *Pain*. 2010;149(2):338–44.
10. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162–73.
11. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12.
12. Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Arch Phys Med Rehabil*. 2007;88(12):1547–60.
13. Chandra K, Shafiq N, Pandhi P, Gupta S, Malhotra S. Gabapentin versus nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial – the GONIP Trial. *Int J Clin Pharmacol Ther*. 2006;44(8):358–63.
14. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med*. 1999;159(16):1931–7.
15. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;(4):CD007938.
16. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 21. [Interoffice memorandum from Atul Pande to John Boris, re: “Gabapentin Approvals”, and handwritten response]; 28 March 1995:X029227.
17. United States Department of Justice. Warner-Lambert to pay \$430 million to resolve criminal & civil health care liability relating to off-label promotion (http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm, accessed 22 March 2017).
18. Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. 2006;145(4):284–93.
19. Saris P. United States Department of Justice. Findings of fact and conclusions of law. In re Neurontin marketing and sales practices litigation. Civil Action No. 04-cv-10739-PBS, 2010 WL 4325225. 2010.
20. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med*. 2009;361(20):1963–71.
21. Vedula SS, Li T, Dickersin K. Differences in reporting of analyses in internal company documents versus published trial reports: comparisons in industry-sponsored trials in off-label uses of gabapentin. *PLoS Med*. 2013;10(1):e1001378.

22. Vedula SS, Goldman PS, Rona IJ, Greene TM, Dickersin K. Implementation of a publication strategy in the context of reporting biases. A case study based on new documents from Neurontin litigation. *Trials*. 2012;13:136.
23. Dickersin K. Reporting and other biases in studies of Neurontin for migraine, psychiatric/bipolar disorders, nociceptive pain, and neuropathic pain. August 2008 (https://www.researchgate.net/publication/228387552_Reporting_and_other_biases_in_studies_of_Neurontin_for_migraine_psychediatricbipolar_disorders_nociceptive_pain_and_neuropathic_pain, accessed 22 March 2017).
24. Neuropathic pain in adults: pharmacological management in non-specialist settings. London: National Institute for Health and Care Excellence; 2014 (Clinical Guideline CG173).
25. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113–e88.
26. International Medical Products Price Guide. Arlington, VA: Management Sciences for Health; 2015 (<http://mshpriceguide.org/en/search-results-by-name-2/?searchYear=2015&searchString=Gabapentin&searchType=Name>, accessed 22 March 2017)

