Tramadol

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 > 2.2. Opioid analgesics

EMLc | Codes ATC: N02AX02

Indication	Chronic cancer pain Code ICD11: ML00.10
INN	Tramadol
Type de médicament	Chemical agent
Type de liste	Liste de base (EML) (EMLc)
Formulations	Oral > Liquid: 100 mg per mL (hydrochloride) Oral > Solid: 50 mg (hydrochloride) immediate release ; 50 mg (hydrochloride) controlled release ; 100 mg (hydrochloride) controlled release ; 150 mg (hydrochloride) controlled release ; 200 mg (hydrochloride) controlled release ; 300 mg (hydrochloride) controlled release ; 400 mg (hydrochloride) controlled release Parenteral > General injections > unspecified: 50 mg per mL in 2 mL ampoule (hydrochloride)
Historique des statuts LME	Demande refusée en 2017 (TRS 1006)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
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	Tramadol
DrugBank	Tramadol

Recommandation du comité d'experts

The Committee acknowledged the issues relating to availability of morphine in LMICs, and the differences in the controls to which morphine and tramadol are subject. The Expert Committee considered that the evidence presented in the application shows tramadol to be a suboptimal treatment for cancer pain compared with morphine and other opioids. The Expert Committee therefore did not recommend the addition of tramadol as a treatment for cancer pain to the EML or EMLc.

Contexte

The application proposed the addition of tramadol to the EML and EMLc for treatment of cancer pain. The proposal formed part of a comparative review of methadone, fentanyl and tramadol for the treatment of cancer pain. Tramadol had not previously been considered for inclusion on the EML/EMLc. Opioid analgesics included on the EML are codeine and morphine. Only morphine is listed on the EMLc. Hydromorphone and oxycodone are considered as alternatives to morphine under a square box listing.
Tramadol is a synthetic opioid agonist with affinity for mu-opioid receptors. It also has non-opioid properties, through inhibition of serotonin and norepinephrine reuptake, which are thought to contribute to its analgesic effect (1). It is less potent than morphine: relative potency of morphine to tramadol is reported as around 4:1 or 5:1 with oral dosing and 10:1 with parenteral dosing (2, 3).

Pertinence pour la santé publique

Cancer is one of the leading causes of morbidity worldwide, with approximately 14 million new cases in 2012 (4). Pain is a frequent and debilitating feature of cancer, occurring across all phases from diagnosis to palliation (5, 6). It is estimated that 31.8% of patients with cancer are undertreated for pain (7). Opioid therapy is the cornerstone of cancer pain management. The burden of cancer is particularly high in low- and middle-income countries (LMICs), where 70% of deaths from cancer occur. Patients living in these countries often have limited access to morphine, the strong opioid of choice for management of moderate to severe cancer pain. This application proposed tramadol as a treatment alternative to morphine to help increase access to opioid pain relief for cancer patients. It noted that, while the available evidence on the use of tramadol in cancer pain is poor, oral tramadol is often available in countries where morphine is not (because of international control, regulatory scheduling, licensing and other restrictions). Access to adequate opioids to deliver appropriate pain management is poor or nonexistent in many countries, particularly LMICs (8, 9).

Bénéfices

The application presented the findings of a search of the literature published in the past five years on tramadol and cancer pain. One study randomized 240 opioid-naive patients with cancer to receive either a weak opioid (tramadol, tramadol in combination with paracetamol, or a fixed-dose combination of paracetamol and codeine) or low-dose oral morphine for 28 days (10). The primary endpoint was the number of "responders" at 28 days or the end of observation, whichever came first. Responders were defined as patients who experienced a 20% or greater reduction in pain intensity from baseline. The primary end-point was achieved in 88.2% of the morphine group and 54.7% of the weak opioid groups (odds ratio (OR) 6.18; 95% confidence interval (should read (CI) 3.12 – 12.24; $P < 0.001$). A systematic review of randomized trials on the effectiveness of opioids for cancer pain, in which pain relief was the primary outcome measure, found that there was poor evidence for the efficacy of tramadol (11). The conclusion was based on three low-quality studies. In a prospective open-label study, the efficacy of a fixed-dose combination of tramadol and paracetamol was evaluated in 353 advanced cancer patients (12). The combination was found to be effective in the treatment of chronic cancer pain, with acceptable tolerability. Average pain scores were significantly lower from 24 hours after the start of treatment. The evidence presented in the application for tramadol was highly heterogeneous: the different comparisons, outcome measures and effect scales used made it difficult to accurately determine the magnitude of benefit.

Torts

The adverse effects commonly associated with opioid therapy are also seen with tramadol, including sedation, constipation and respiratory depression. Severe respiratory depression associated with tramadol has been reported in children (13) and in one case report of an adult with cancer pain and renal insufficiency (14). Hyponatraemia has also been observed during tramadol treatment (15–17). At normal doses, tramadol has been associated with seizures (18). Serotonin toxicity may occur when tramadol is given concomitantly with, or within 14 days of, monoamine oxidase inhibitors and other medicines that increase serotonin activity (19). Tramadol abuse and trafficking have become a serious problem in many countries where the drug is widely available and not subject to stricter controls, particularly in Africa and the Middle East and in parts of Asia, as noted in the 2015 report of the United Nations International Narcotics Control Board (20).

Preuves supplémentaires

In a randomized controlled trial (RCT) that compared morphine with weak opioids for moderate cancer pain, both treatments were found to be well tolerated (10). No differences were observed in the intensity and frequency of opioid-related effects between treatment groups, and there were few discontinuations due to adverse events. In another RCT, tramadol 200 mg/day was compared with hydrocodone + acetaminophen 25 mg + 2500 mg/day in 118 patients with chronic cancer pain (21). There was no statistically significant difference between the two treatment arms in terms of analgesic efficacy. However, the incidence of side-effects such as nausea (relative risk (RR) 1.69; 95% CI 1.03–2.77), vomiting (RR 2.21; 95% CI 1.14–4.32) and dizziness (RR 2.12; 95% CI 1.17–3.86) was significantly higher in the tramadol arm. Similar results were found in another RCT which compared the incidence of adverse events associated with oral tramadol, hydrocodone and codeine in 177 patients with cancer pain (22). The abuse potential of tramadol, both in experienced drug users and in patients with no history of substance abuse, has been raised in recent studies (23, 24).

Rapport coût/efficacité

No information regarding costs or cost–effectiveness was provided in the application. The MSH (Management Sciences for Health) International Medical Products Price Guide reports a median unit price for tramadol hydrochloride 50-mg tablet/capsule of US$ 0.0427. The median unit price for morphine sulfate 10-mg tablet or capsule is reported as US$ 0.1247 (26)

Directives de l'OMS

The WHO guidelines for management of cancer pain are currently under review. WHO's 2012 guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (25) recommend the use of strong opioid analgesics for the relief of moderate to severe persisting pain in children (strong recommendation, low-quality evidence). Morphine is recommended as the first-line treatment choice. There is insufficient evidence to support a recommendation of alternative opioids as first choice. The guidelines also recommend switching opioids and/or route of administration in the event of inadequate analgesic effect with intolerable side-effects (strong recommendation, lowquality evidence). Alternative opioids listed in the guidelines are fentanyl, hydromorphone, methadone and oxycodone. Oral administration is recommended.

Disponibilité

Unlike morphine, tramadol is not subject to international control under the Single Convention on Narcotic Drugs, 1961. Preliminary results (unpublished) of a price and availability survey conducted by WHO in the Democratic Republic of the Congo indicated that controlled-release oral morphine was available in only 1 of 85 facilities sampled, while immediate-release morphine was not available in any of them. In comparison, immediateand controlled-release tramadol was available in 26 and 11 of the 85 facilities sampled, respectively.

Autres considérations

WHO is currently developing new cancer pain guidelines which are due for completion in late 2017 or early 2018.

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