




Fentanyl

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

Codes ATC: N02AB03

Indication	Other specified chronic cancer related pain	Code ICD11: MG30.1Y
INN	Fentanyl	
Type de médicament	Chemical agent	
Type de liste	Liste de base	
Formulations	Oral > Solid: 100 to 800 µg sub-lingual tablet (as citrate) ; 200 to 1600 µg lozenges (as citrate) Oral > Other: 200 to 1200 µg buccal film (as citrate)	
Historique des statuts LME	Demande refusée en 2023 (TRS 1049)	
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	Fentanyl 	
DrugBank	Fentanyl 	

Recommandation du comité d'experts

The Expert Committee acknowledged that most cancer patients with active cancer develop pain during the course of the disease, and that pain is one of the most feared consequences of cancer for both patients and their families. The Committee noted that the EML currently includes immediate-release formulations of oral morphine, which is recognized as the strong opioid of choice for breakthrough cancer pain. The Committee also acknowledged the serious problems with access to morphine in many parts of the world. The Committee acknowledged that the evidence presented in the application shows oral transmucosal fentanyl (on a background of regular opioid dosing) to be an effective option for the treatment of breakthrough cancer pain. When compared with immediate-release morphine, oral transmucosal fentanyl might provide some advantage in terms of lower pain intensity and better pain relief scores. However, the Committee noted that most studies compared oral transmucosal fentanyl to placebo and therefore these data did not provide compelling evidence of the superiority of transmucosal fentanyl compared with other fast-acting opioids, including immediate-release oral morphine which is already included on the Model List. The Committee considered that any advantages of oral transmucosal fentanyl are easily off-set by several safety concerns. Fentanyl has an estimated 50 to 100 times greater potency than morphine, has more complex pharmacokinetics and is associated with greater potential for drug-drug interactions – factors that necessitate specialist training for its safe and appropriate use, which may not be widely available in low- and middle-income settings. The Committee also recognized that access to immediate-release oral morphine in many settings is limited, meaning that the necessary background opioid treatment required for appropriate use of oral transmucosal fentanyl may not be available, further compromising its safe and appropriate use. Furthermore, while opioid misuse is reported to be uncommon in patients with cancer, fentanyl has a higher addictive potential than other opioids and has been associated with increased trends

in opioid overdose deaths in non-medical users of opioids in several countries. The Committee noted a lack of cost-effectiveness data comparing oral transmucosal fentanyl with immediate-release morphine, but considered that oral transmucosal fentanyl is more costly than oral morphine, which is not matched by commensurate therapeutic benefits. Therefore, the Expert Committee did not recommend the addition of oral transmucosal fentanyl to the EML for use in the treatment of breakthrough cancer pain in adults based on the lack of evidence of superiority over already listed immediate-release morphine, safety concerns and lack of compelling cost-effectiveness data.

Contexte

Oral transmucosal formulations of fentanyl have not previously been considered for inclusion in the EML. In 2017, fentanyl transdermal patches were included on the EML for the management of chronic cancer pain. While intravenous morphine was included on the first list in 1977, immediate-release formulations of oral morphine have been included on the EML (tablets and oral liquid) since 1984. Hydromorphone and oxycodone are included as alternatives to morphine under a square box listing.

Pertinence pour la santé publique

Cancer is a major public health problem worldwide and is the second leading cause of death, accounting for an estimated 9.9 million deaths and more than 19 million new cases in 2020 (1). The cancer burden continues to grow globally, with an estimated doubling of the yearly incidence by 2040, and places tremendous physical, emotional and financial strain on individuals, families, communities and health systems (2,3). Despite this growth in incidence, the number of deaths from cancer is decreasing annually because more patients are benefiting from early detection and new improved treatments (4). More than 80% of patients with cancer develop pain before death, and pain is one of the most feared consequences of cancer for both patients and families (5). Moderate-to-severe pain has been reported in 38% of the cases (6). This pain is often assessed at 7 or higher in the numeric rating scale (with 0 being no pain and 10 the worst pain imaginable) (7). Breakthrough cancer pain is a transient exacerbation of pain in the context of otherwise adequately controlled background pain. An accurate estimate of the prevalence of breakthrough cancer pain is not available. A systematic review and meta-analysis of 19 observational studies (6065 participants) reported a pooled prevalence rate of breakthrough cancer pain of 59.2% (95% confidence interval (CI) 58.0% to 60.4%, high heterogeneity). Subgroup analysis found that the lowest and highest pooled prevalence rates were reported in studies conducted in the outpatient setting (39.9%, 95% CI 35.8% to 44.0%) and hospice setting (80.5%, 95% CI 77.9% to 83.1%) (8). Breakthrough cancer pain can occur as a direct consequence of the tumour (70–80% of cases), as a result of cancer therapy (10–20% of cases) or be unrelated to the tumour or treatment (< 10% cases) (9). Breakthrough pain has a significant impact on the quality of life of patients, being associated with more severe pain-related functional impairment and psychological distress (10,11). It is also associated with high use of health care resources, mainly related to a higher number of hospital admissions and drug costs (12,13).

Bénéfices

A 2013 Cochrane systematic review of 15 randomized trials (1699 participants) evaluated the efficacy of opioid analgesics compared with placebo or active comparator for management of breakthrough cancer pain (14). The studies included reported on seven different transmucosal fentanyl formulations – five administered orally and two administered nasally. Eight studies compared the transmucosal fentanyl formulations with placebo, four studies compared them with another opioid, one study was a comparison of different doses of the same formulation and two were randomized titration studies. For the comparison of transmucosal fentanyl versus placebo, transmucosal fentanyl was significantly superior to placebo for pain intensity difference at 10 minutes (mean difference (MD) 0.39, 95% CI 0.27 to 0.52; six studies, 988 participants), and at 15 minutes (MD 0.49, 95% CI 0.35 to 0.62; seven studies, 538 participants). No significant difference was observed at 30 minutes (MD 0.92, 95% CI 0.75 to 1.09; seven studies, 538 participants). For the comparison of transmucosal fentanyl versus oral morphine, the point estimate in the mean pain intensity difference at 15 minutes favoured fentanyl, but this was not statistically significant (MD 0.37, 95% CI 0.00 to 0.73; two studies, 308 participants). Similarly, for the comparison of oral transmucosal fentanyl citrate versus intravenous morphine, the point estimate for mean pain intensity difference at 15 minutes favoured fentanyl, but was not statistically significant (MD 0.80, 95% CI 0.00 to 1.60; one study, 50 participants). Results for other time points for comparisons with oral and intravenous morphine were not reported. Brief summaries of the results of eight trials from the 2013 Cochrane review, considered by the applicants to be relevant to the application, are presented below. A randomized, placebo-controlled, double-blind study evaluated oral transmucosal fentanyl citrate for treatment of breakthrough pain in 93 adult patients with cancer (15). After

titration to an effective fentanyl dose, participants were given 10 randomly ordered treatment units (seven fentanyl, three placebo). Of 804 breakthrough pain episodes treated, 247 were with placebo and 557 were with fentanyl. Episodes of breakthrough pain treated with fentanyl had significantly larger changes in pain intensity and better pain relief at all time points (15, 30, 45 and 60 minutes) than episodes treated with placebo. Episodes of breakthrough pain treated with placebo required the use of rescue medication significantly more often than episodes treated with fentanyl (34% versus 15%; relative risk (RR) 2.27, 95% CI 1.51 to 3.26). Two randomized trials compared fentanyl buccal tablet with placebo in patients with breakthrough cancer pain (16,17). In the first study, after an open-label titration phase to determine effective dose, 77 patients were randomly assigned to receive a prespecified dose sequence of 10 tablets (seven fentanyl, three placebo). Of 701 breakthrough pain episodes treated, 208 were with placebo and 493 were with fentanyl. The primary outcome measure was the summed pain intensity difference at 30 minutes. Mean summed pain intensity difference at 30 minutes (standard error (SE)) was significantly greater for buccal fentanyl (3.0 (SE 0.12)) than for placebo (1.8 (SE 0.18)). For other outcome measures including pain relief, pain intensity difference, summed pain intensity differences and summed total pain relief and patient ratings of global performance, results all significantly favoured buccal fentanyl (16). The second study, of similar design, included 87 patients in the double-blind phase. The primary outcome measure was summed pain intensity difference at 60 minutes, which significantly favoured buccal fentanyl compared to placebo – 9.7 (SE 0.63) versus 4.9 (SE 0.50). Pain intensity differences and pain relief also significantly favoured buccal fentanyl at all time points (17). A randomized phase II study evaluated efficacy and tolerability of sublingual fentanyl tablets in 27 patients with breakthrough cancer pain (18). Participants received placebo, fentanyl 100 micrograms, 200 micrograms and 400 micrograms in random order at four breakthrough pain episodes. The primary efficacy measure was pain intensity difference; overall, the difference was significantly larger with 400 micrograms of fentanyl compared with placebo, and improved pain relief was reported for 100 micrograms and 200 micrograms of fentanyl, although this was not statistically significant. The 400 microgram strength was also associated with significantly reduced use of rescue medication and improved global assessment of treatment. A randomized placebo-controlled, phase III study evaluated efficacy and tolerability of sublingual fentanyl orally disintegrating tablet for breakthrough cancer pain, with 61 patients included in the primary efficacy analysis (19). Following a 2-week open-label titration phase, participants received fentanyl or placebo in random order. For the primary efficacy measure of summed pain intensity difference at 30 minutes, there was a significant improvement for fentanyl compared with placebo (49.5 versus 36.6, $P = 0.0004$). Treatment was also associated with significant improvements in pain intensity difference and pain relief at time points from 10 minutes after dose administration. A similar study evaluated the efficacy and tolerability of fentanyl buccal soluble film formulation in 80 adults with breakthrough cancer pain (20). Mean summed pain intensity difference at 30 minutes was significantly greater for episodes treated with fentanyl compared with placebo, with significant differences maintained to the last assessed time point of 60 minutes. Pain relief values for fentanyl were significantly better than placebo at 30 minutes after dose administration, and the percentage of pain episodes with a 33% or 50% decrease in pain was also significantly greater with fentanyl than placebo. A randomized, double-blind, double-dummy, multiple crossover trial compared oral transmucosal fentanyl and immediate-release morphine sulfate in 93 adults with breakthrough cancer pain (21). After an open-label dose titration phase, participants received 10 prenumbered sets of randomized capsules and oral transmucosal units (5 x successful fentanyl dose + 5 x placebo, 5 x successful morphine dose + 5 x placebo). Oral transmucosal fentanyl performed significantly better than immediate-release morphine for efficacy measures including pain intensity, pain intensity difference and pain relief at all time points. Global performance rating scores also significantly favoured fentanyl. Significantly more pain episodes treated with oral transmucosal fentanyl had a greater than 33% change in pain intensity score at 15 minutes than episodes treated with immediate-release morphine (42.3% versus 31.8%, $P < 0.001$). A randomized, double-blind dose titration study in ambulatory cancer patients evaluated safety and efficacy of increasing doses of oral transmucosal fentanyl for treatment of breakthrough cancer pain (22). This study was not designed to compare fentanyl with usual opioid rescue medicines, however exploratory analyses were performed. These analyses showed that fentanyl treatment was associated with significantly greater analgesic effects at time points up to 60 minutes, and a more rapid onset of effect than usual rescue opioids. Participants rated the global satisfaction of oral transmucosal fentanyl citrate significantly higher than global performance of their usual opioid rescue medicine (2.74 versus 2.09, $P = 0.0002$). The following studies were not included in the 2013 Cochrane review. A mixed-treatment meta-analysis of five randomized trials indirectly compared fentanyl preparations, morphine and placebo for the treatment of breakthrough cancer pain to determine the relative contributions to pain relief from oral morphine and the fentanyl preparations using placebo as the common comparator (23). The overall probability of superior pain relief, as measured by differences in pain intensity difference scores, compared with placebo was calculated for 15- to 60-minute intervals after dosing. For the first 30 minutes after dosing, the probabilities of superiority over placebo were 56%, 83%, 66% and 73% for immediate-release morphine, fentanyl buccal tablet,

fentanyl orally disintegrating tablet and fentanyl lozenge, respectively. Comparing fentanyl preparations with immediate-release morphine over the first 30 minutes after dosing, the probabilities of superiority over morphine were estimated to be 58% for buccal tablet, 56% for orally disintegrating tablet and 62% for lozenge. The long-term effectiveness of fentanyl orally disintegrating tablets for treatment of breakthrough cancer pain was assessed in a non-randomized, open-label, phase III study (139 participants) (24). Effectiveness was evaluated at screening for participation and at each monthly visit using patients' global evaluation of medication, the brief pain inventory and the depression, anxiety and positive outlook scale. Evaluation of patient satisfaction using the patients' global evaluation of medication measure showed an increase in satisfaction ("very satisfied" or "satisfied") with study pain medication at the end of the study (12 months) versus time at study enrolment (77% versus 54%). For quality-of-life measures, the brief pain inventory evaluation of pain severity indicated that mean levels of pain generally remained stable throughout the study, except for current pain, which was significantly lower at the 6-month visit, compared with at screening. Mean brief pain inventory scores for pain relief improved significantly at both the 6-month and end-of-study visits, compared with at screening. Brief pain inventory scores for interference of pain with daily functioning decreased over the study period, suggesting improvement. The scores on the depression, anxiety and positive outlook scale showed numerical trends towards improvement in all three quality-of-life domains (depression, anxiety and well-being) at the end of the study, compared with at screening. Improvement in depression scores at 6 months was statistically significant. Subgroup analyses from a multicentre, prospective, observational, open-label study assessed the effect of fentanyl sublingual tablets in the management of breakthrough pain in patients with cancer according to age (< 65 and ≥ 65 years), measuring pain intensity, onset of pain relief, frequency and duration of breakthrough pain episodes, and adverse events at 3, 7, 15 and 30 days. Health-status tools used were the Short Form 12, version 2 questionnaire, and the Hospital Anxiety and Depression Scale (25). Self-reported levels of pain intensity improved significantly compared with baseline for all assessment points and both subgroups. For each assessment point, reduction in pain intensity was greater in the younger age group (67.3% reduction versus 56.3% reduction). A randomized, open-label study compared the efficacy and safety of oral transmucosal fentanyl and oral morphine in Indian patients (186 participants) (26). Primary efficacy endpoints were reduction in pain determined by numerical rating scale at 5, 15, 30 and 60 minutes, and percentage of breakthrough pain episodes showing at least 33% reduction in pain intensity at 15 minutes. Patients treated with fentanyl experienced significantly greater reduction in pain intensity of breakthrough episodes compared with those treated with oral morphine at all time points assessed. The percentage of breakthrough pain episodes with more than 33% reduction in pain intensity at 15 minutes was significantly greater in patients treated with fentanyl compared with patients treated with morphine (56% versus 39%). Efficacy and safety studies of oral transmucosal fentanyl versus placebo conducted in the Japanese population also showed positive results (27,28).

Torts

The adverse effects of fentanyl citrate are generally consistent with the known adverse effects of potent opioid analgesics (14). The most commonly reported adverse effects associated with fentanyl formulations in the treatment of breakthrough cancer pain reported across various studies include asthenia, constipation, dizziness, headache, nausea, pruritus, somnolence and vomiting (15–19,21,22). Studies with transmucosal fentanyl citrate have shown no differences in pharmacokinetic parameters between younger and older people, and so dose modification is not considered necessary for elderly patients (29). An alert published in 2018 by the Spanish Medicines Agency reported that almost 60% of the cases of abuse and/or dependence reported to the Spanish Pharmacovigilance System involved patients in whom immediate-release fentanyl was used for off-label indications. A systematic review of the literature found an overall incidence of addiction of up to 50% in non-oncology patients, while in oncology patients it was up to 7.7%. In the context of trials evaluating new presentations of rapid-acting fentanyl, 11% of patients were found to have aberrant behaviour associated with its use, of whom < 1% were found to be addicted (30).

Rapport coût/efficacité

Breakthrough cancer pain imposes a significant financial burden on patients and health systems through increased hospitalization and health care utilization (12,32). An economic analysis of oral fentanyl formulations for treatment of breakthrough cancer pain was conducted from the Italian national health services perspective (33). The base-case analysis found that compared with placebo, all formulations assessed (sublingual fentanyl citrate, fentanyl sublingual tablets, fentanyl buccal soluble film, fentanyl buccal tablet and oral transmucosal fentanyl citrate) were associated with incremental costs per quality-adjusted life year gained lower than €50 000–60 000, the incremental cost–effectiveness ratio threshold generally used in Italy. Among formulations, sublingual fentanyl citrate dominated all others (lower cost, greater effectiveness). An economic analysis from Sweden evaluated

the cost-effectiveness of intranasal fentanyl spray compared with oral transmucosal fentanyl citrate and fentanyl buccal tablet for the treatment of breakthrough cancer pain (34). The base-case analysis found that compared with placebo, all formulations assessed were associated with incremental costs per quality-adjusted life year gained lower than the willingness-to-pay threshold in Sweden of €45 000. The application presented estimates of annual treatment costs of transmucosal fentanyl by country and region. Average national treatment costs per patient per year calculated in the application based on the defined daily dose for sublingual fentanyl of 600 micrograms ranged from US\$ 189.70 in Egypt to US\$ 48 386.40 in Lebanon. Average treatment costs per patient per year by region based on the defined daily dose of 600 micrograms were reported in the application as US\$ 4695.60 in Africa, US\$ 6455.50 in Asia and the South Pacific, US\$ 5673.10 in Europe, US\$ 28 534.30 in North America and US\$ 3214.60 in South America.

Directives de l'OMS

The 2018 WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents includes the best practice statement, “breakthrough pain should be treated with a rescue medicine, which should be an opioid such as morphine in its immediate-release formulation” (31). The WHO Guideline Development Group considered a single small randomized controlled trial (68 participants) which compared analgesics specifically for management of breakthrough pain in an older population with multiple cancer types. The trial provided low strength of evidence that the choice between sustained-release and immediate-release morphine may make no difference in preventing breakthrough pain or reducing pain. The trial did not report on pain relief speed, pain relief maintenance, quality of life, functional outcomes or respiratory depression. The Guideline Development Group agreed that they could not justify making a recommendation on the basis of only one eligible low-quality trial that looked at too few of the options that were clinically available. However, given the urgent need for guidance to manage breakthrough pain for both patients and clinicians, the Guideline Development Group decided to make a best practice statement that breakthrough pain should always be relieved with rescue medicine based on clinical experience and patient need. The Guideline Development Group highlighted that the cost of certain formulations, such as transmucosal fentanyl, was likely to be prohibitively expensive for some low- and middle-income settings, and that cheaper medicines, such as immediate-release oral morphine, should be made available as a priority if they were not already available (31).

Disponibilité

The application reported that 24 brands (innovator and generic) of transmucosal fentanyl formulations were variously available in 47 countries globally. Availability in low- and middle-income countries appears limited.

Autres considérations

The Expert Committee noted the comments received during the public consultation period in relation to the application from the International Association for Hospice and Palliative Care, the Worldwide Hospice Palliative Care Alliance, the Groupe de Recherche et d'Actions Sociales in Burkina Faso and the WHO Collaborating Centre for Training and Policy on Access to Pain Relief. These stakeholders all expressed their opposition to the proposed inclusion of oral transmucosal fentanyl on the Model List, citing the following reasons. • Patients must remain on around-the-clock opioids while taking oral transmucosal fentanyl citrate. Given the limited availability of opioids for pain and palliative care in resource-constrained settings, it would be challenging to meet these requirements in low- and middle-income countries. • Morphine (with oxycodone and hydromorphone as alternatives) is already included in the EML. The inclusion of both immediate-release and sustained-release oral preparations enables morphine to be successfully used in both acute and chronic cancer pain, and breakthrough pain. Morphine is the strong opioid of choice for treatment of moderate-to-severe pain. No evidence exists to support the need for, or the addition of, another pure agonist to treat breakthrough pain. • Data are lacking on dose-equivalence for transmucosal fentanyl compared with other opioids and oral, modified-release formulation of fentanyl. This means that using transmucosal fentanyl to commence or titrate opioids to effect is less safe than the usual, recommended practice of immediate- and modified-release morphine (or equivalent opioids). • Because of its rapid onset and lipophilic characteristics with selective activity for μ -receptors expressed in the brain, spinal cord and other tissues, fentanyl citrate has a higher risk of non-medical use compared with the other pure agonists included in the WHO EML. Its short time to onset should be considered of equal importance to its short duration of action. In many cases, patients using fentanyl citrate for breakthrough pain often consume more opioid in total over a 24-hour period than if they had been prescribed their usual regimen of immediate-release with or without modified release morphine (or equivalent longer-acting opioids) for breakthrough

pain. • Oral transmucosal fentanyl citrate is available in only a few, mostly high-income, countries. Appropriate use of oral transmucosal fentanyl may not be feasible in low-income settings, where health care workers may not receive training in the administration and pharmacokinetics of fentanyl, which could lead to serious adverse events and potential fatalities. • The cost-effectiveness of oral transmucosal fentanyl versus immediate-release morphine is not known. Inclusion of oral transmucosal fentanyl on the EML may result in the allocation of public funds for the procurement of an expensive formulation in lieu of more cost-effective formulations already included in the list. • Breakthrough pain is not homogenous and whilst transmucosal fentanyl has a place in treating some types of breakthrough pain and for some patients, it does not and must not replace immediate-release morphine.

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer*. 2021;149(4):778–89.
2. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/330745>, accessed 6 October 2023).
3. Las cifras del cáncer en España 2020 [Cancer figures in Spain 2020]. Barcelona: Sociedad Española de Oncología Médica; 2020.
4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33.
5. Bruera E, Kim HN. Cancer pain. *JAMA*. 2003;290(18):2476–9.
6. Van Den Beuken-Van MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage*. 2016;51(6):1070–90.
7. Woo A, Lechner B, Fu T, Wong CS, Chiu N, Lam H, et al. Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: a literature review. *Ann Palliat Med*. 2015;4(4):176–83.
8. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manage*. 2014;47(1):57–76.
9. Alamo Gonzalez C, Cabezon Gutiérrez L, Proyecto ADAPTA Gdt. Adapta project: adequacy of treatment in breakthrough cancer pain. *Rev Soc Esp Dolor*. 2019;26(1):31–43.
10. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81(1–2):129–34.
11. Narayana A, Katz N, Shillington AC, Stephenson JJ, Harshaw Q, Frye CB, et al. National breakthrough pain study: prevalence, characteristics, and associations with health outcomes. *Pain*. 2015;156(2):252–9.
12. Pérez-Hernández C, Jiménez-López AJ, Sanz-Yagüe A, Mar-Medina J, Larrañaga I, Soler-López B. Observational study evaluating the economic impact of breakthrough pain in cancer patients in clinical practice in Spain: the IMDI study. *Pain Ther*. 2018;7(2):227–40.
13. Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manage*. 2013;46(5):619–28.
14. Zeppetella G, Davies AN. Opioids for the management of breakthrough pain in cancer patients. *Cochrane Database Syst Rev*. 2013(10):CD004311.
15. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for treatment of breakthrough pain in cancer patients. *J Natl Cancer Inst*. 1998;90(8):611–6.
16. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain*. 2006;22(9):805–11.
17. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Support Oncol*. 2007;5(7):327–34.
18. Lennernäs B, Frank-Lissbrant I, Lennernäs H, Kälkner KM, Derrick R, Howell J. Sublingual administration of fentanyl to cancer patients is an effective treatment for breakthrough pain: results from a randomized phase II study. *Palliat Med*. 2010;24(3):286–93.
19. Rauck RL, Tark M, Reyes E, Hayes TG, Bartkowiak AJ, Hassman D, et al. Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. *Curr Med Res Opin*. 2009;25(12):2877–85.
20. Rauck R, North J, Gever LN, Tagarro I, Finn AL. Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. *Ann Oncol*. 2010;21(6):1308–14.
21. Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain*. 2001;91(1–2):123–30.
22. Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al. Oral transmucosal fentanyl citrate (otfc) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain*. 1999;79(2–3):303–12.
23. Jandhyala R, Fullarton JR, Bennett MI. Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: a meta-analysis of comparative trials. *J Pain Symptom Manage*. 2013;46(4):573–80.
24. Nalamachu S, Hassman D, Wallace MS, Dumble S, Derrick R, Howell J. Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain. *Curr Med Res Opin*. 2011;27(3):519–30.
25. Guítart J, Vargas MI, De Sanctis V, Folch J, Salazar R, Fuentes J, et al. Breakthrough pain management with sublingual fentanyl tablets in patients with cancer: age subgroup analysis of a multicenter prospective study. *Drugs R D*. 2017;17(3):419–25.
26. Bhatnagar S, Devi S, Vinod N, Jain P, Durgaprasad G, Maroo SH, et al. Safety and efficacy of oral transmucosal fentanyl citrate compared to morphine sulphate immediate release tablet in management of breakthrough cancer pain. *Indian J Palliat Care*. 2014;20(3):182–7.
27. Kosugi T, Hamada S, Takigawa C, Shinozaki K, Kunikane H, Goto F, et al. A randomized, double-blind, placebo-controlled study of fentanyl buccal tablets for breakthrough pain: efficacy and safety in Japanese cancer patients. *J Pain Symptom Manage*. 2014;47(6):990–1000.
28. Shimoyama N, Gomyo I, Katakami N, Okada M, Yukitoshi N, Ohta E, et al. Efficacy and safety of sublingual fentanyl orally disintegrating tablet at doses determined by titration for the treatment of breakthrough pain in Japanese cancer patients: a multicenter, randomized, placebo-controlled, double-blind phase III trial. *Int J Clin Oncol*. 2015;20(1):198–206.
29. Moya Riera J, Murillo González M, Rodríguez Mesa D, Escobar Álvarez Y. Fentanilo en el dolor irruptivo oncológico [Fentanyl for breakthrough cancer pain]. *Rev Soc Esp Dolor*. 2013;20(3):137–41.
30. Blázquez Puerta A, Chacón Coronado AM, De Juan Roldán JI, Esteban Bueno G, Guerrero García FJ, Lozano Prieto PP, et al. Fentanilo de acción rápida: Indicaciones, diagnóstico y abordaje de problemas relacionados con su uso [Fast-acting fentanyl: indications, diagnosis and addressing problems related to its use]. *Med Fam Andal*. 2020;21(1 Suppl):30–43.
31. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/279700>, accessed 6 October 2023).
32. Kuo K-L, Saokaew S, Stenehjem DD. The pharmacoeconomics of breakthrough cancer pain. *J Pain Palliat Care Pharmacother*. 2013;27(2):167–75.
33. Cortesi PA, D'Angiolella LS, Vellucci R, Allegri M, Casale G, Favaretti C, et al. Cost-effectiveness analysis of oral fentanyl formulations for breakthrough cancer pain treatment. *PLoS One*. 2017;12(6):e0179523.
34. Vissers DCJ, Lenre M, Tolley K, Jakobsson J, Sendersky V, Jansen JP. An economic evaluation of short-acting opioids for treatment of breakthrough pain in patients with cancer. *Value Health*. 2011;14(2):274–81.

