

## Sublingual Fentanyl (Abstral®) for Breakthrough Cancer Pain

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### Abstract

The sublingual fentanyl tablet is indicated for the management of breakthrough pain in patients with cancer who are already receiving opioid therapy for their background cancer pain. The pharmacokinetic, efficacy, tolerability and safety profile of the sublingual fentanyl tablet suggests that it has a valuable role to play in the symptomatic pharmacological management of breakthrough pain. The effective dose of the sublingual fentanyl tablet cannot be predicted from previous around-the-clock (ATC) or rescue medication; therefore, titration is required to determine the effective dose according to the needs of the individual patient.

### Keywords

Cancer pain, breakthrough pain, fentanyl, palliative care

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Pain is a well recognised feature of cancer that usually becomes more common as the disease progresses.<sup>1</sup> Pain is the most feared of all the cancer symptoms, so effective analgesia is essential to good patient management. Opioids have remained the mainstay of pharmacological management of cancer pain, and a number of studies have demonstrated that pain can be controlled in the majority of patients using the approach recommended by the World Health Organization (WHO);<sup>2</sup> however, even when background pain is well controlled, many patients with advanced cancer may experience brief, self-limiting exacerbations of severe pain known as breakthrough pain.<sup>3</sup>

### Breakthrough Pain

The term breakthrough pain – also described as episodic pain, incidental pain, transient pain, exacerbation of pain and pain flare – is a transient worsening of pain that occurs spontaneously or in relation to a predictable or unpredictable trigger, usually despite ongoing analgesic therapy.<sup>4</sup> The term has been used to describe a phenomenon whereby pain intensity suddenly increases to 'break through' the background pain that is otherwise controlled by a fixed-schedule around-the-clock (ATC) opioid regimen (see *Figure 1*). Breakthrough pain relies on the co-existence of adequately controlled background pain and should therefore be distinguished from end-of-dose pain, which relates to decreasing analgesia levels at the end of the dose interval, usually because of an inadequate analgesic dose or too long an administration interval.

The occurrence of breakthrough pain is an indication of a distinct clinical problem that requires independent assessment and targeted treatment. Breakthrough pain is a heterogeneous entity; the clinical features vary from individual to individual and may vary within an

individual over time. However, in many instances a typical breakthrough pain episode is characterised by a fast onset, is often very severe, usually reaches peak intensity within a few minutes and can last for an average of approximately 30 minutes.<sup>3</sup> Two types of breakthrough pain exist: incident pain, which can be precipitated by predictable volitional factors such as movement or unpredictable non-volitional factors such as bladder spasm; and spontaneous pain, which occurs in the absence of a specific trigger and can be unpredictable and occur at random.<sup>4</sup>

Despite the self-limiting nature of breakthrough pain, it can place significant physical, psychological and economic burdens on both patients and their carers (see *Figure 2*). Patients with breakthrough pain are often less satisfied with their analgesic therapy and have decreased functioning because of their pain, and may also experience social and psychosocial consequences such as increased levels of anxiety and depression.<sup>5</sup> Breakthrough pain can be a poor prognostic indicator, and the site of breakthrough pain may predict the response to treatment. Furthermore, inadequately relieved breakthrough pain can place additional burdens on patients and on the healthcare system.<sup>6</sup> Understanding this impact on the patient's quality of life is important in setting realistic treatment goals.

### Management of Breakthrough Pain

The management of breakthrough pain aims to reduce the frequency and severity of the pain. The basic principles are:

- general assessment;
- detailed pain history;
- lifestyle changes;

- a modification of the pathological processes;
- management of the reversible causes;
- pharmacological and non-pharmacological symptomatic management; and
- re-assessment.

**Current Pharmacological Symptomatic Management**

There is currently no ‘gold standard’ for the pharmacological symptomatic treatment of breakthrough pain. It is important to individualise management, and three principles have been proposed to enable this:<sup>7</sup>

- implementation of primary therapies;
- optimisation of scheduled analgesia; and
- specific analgesia for breakthrough pain.

Given the heterogeneous nature of breakthrough pain, a combination of the above may be required; however, the most common treatment strategy is the use of supplemental analgesia, also known as ‘rescue medication’.

**Rescue Medication**

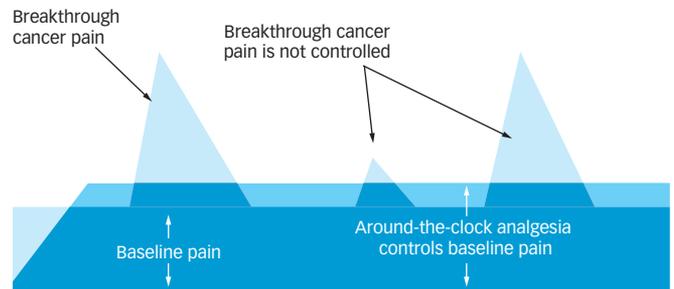
Opioids are the most commonly used rescue medication. A number of factors should be taken into account when selecting the appropriate drug, including the class of drug, the route of administration, the dosage, the patient setting and the breakthrough pain subtype. The ideal rescue medication should be efficacious and patient-friendly, with a rapid onset of action, a relatively short duration of action and minimal adverse effects and must be able to be used either prophylactically (for predictable pain) or as soon as pain starts (for unpredictable pain). In this way, breakthrough pain is rapidly controlled while avoiding opioid accumulation and reducing systemic exposure, hence minimising the incidence of adverse effects.

The most common method of providing rescue medication is with normal-release formulations of morphine. The most effective dose of rescue medication also remains unknown, although a fixed proportion of the ATC is usually advised<sup>8</sup> – typically 10–15% of the daily dose – but this is based on anecdotal evidence only. An oral opioid may take 30–45 minutes to provide relief, whereas the peak pain intensity of breakthrough pain can occur in five to 10 minutes. In addition, medication taken by mouth may be subject to delayed gastric emptying and first-pass hepatic metabolism, the blood–brain barrier presents a final obstacle that delays the onset of action and other oral opioids may have similar limitations.<sup>9</sup> Although the oral route is often preferred for rescue medication, the typical clinical and dynamic characteristics of breakthrough pain suggest that responsiveness to an oral drug may be less than optimal. The potential usefulness for breakthrough pain of a non-parenteral drug with a faster onset of effect was the rationale for the development of oral transmucosal fentanyl citrate as a treatment for breakthrough pain. Controlled studies showed that this formulation could provide analgesia at 15 minutes.<sup>10</sup> There have been efforts to develop other non-parenteral opioid formulations that can provide more rapid, and possibly more effective, relief of breakthrough pain; one such development is the fentanyl sublingual tablet.

**Sublingual Drug Delivery**

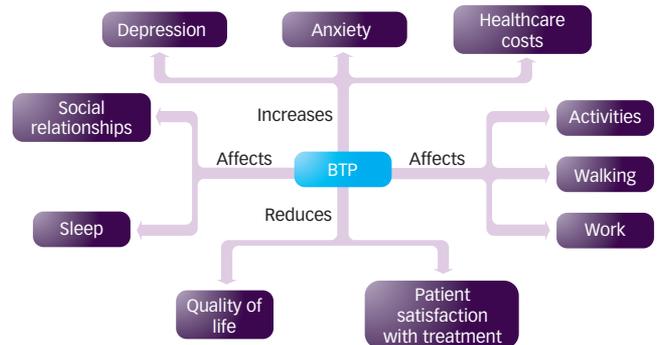
The sublingual space is a primary focus for drug delivery via the oral mucosa because it is highly permeable and highly vascularised. Any

**Figure 1: Breakthrough Pain Graphics**



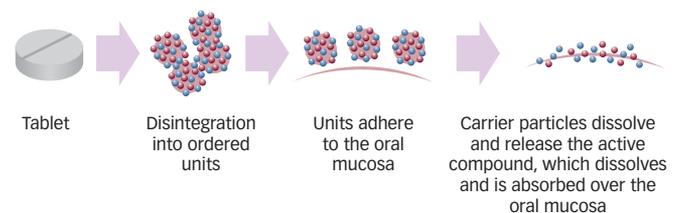
Sources: Bennett et al., 2005,<sup>18</sup> Coluzzi, 1998<sup>19</sup> and Simmonds, 1999.<sup>20</sup>

**Figure 2: Effects of Breakthrough Pain on Patients**



BTP = breakthrough pain. Sources: Portenoy et al., 1999<sup>5</sup> and Caraceni et al., 2004.<sup>21</sup>

**Figure 3: FAST Technology Diagram**



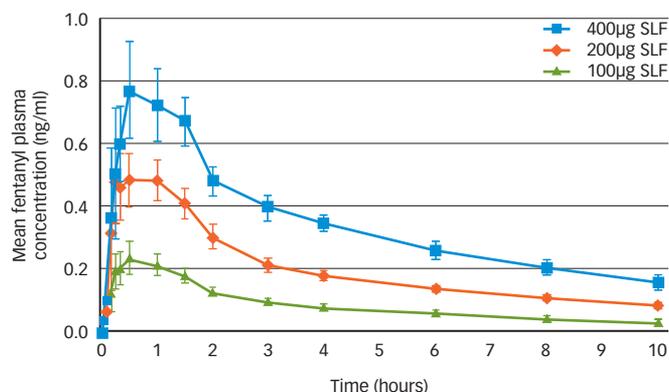
Source: Bredenberg et al., 2003.<sup>11</sup>

drugs diffusing into the oral mucosa membranes have direct access to the systemic circulation via capillaries and venous drainage. Drugs best suited to oral transmucosal administration are those that are potent, lipophilic and ionised at physiological pH; fentanyl is therefore a strong candidate for such a delivery system.

Sublingual fentanyl citrate (SLF; Abstral®) is an oral transmucosal delivery formulation of fentanyl citrate indicated for the management of breakthrough pain in patients already receiving opioid therapy for their background cancer pain. SLF was granted Europe-wide marketing authorisation in June 2008; it was made available in Sweden in August 2008 and in the UK and Germany in January 2009 in six dosing strengths containing 100, 200, 300, 400, 600 and 800µg fentanyl citrate.

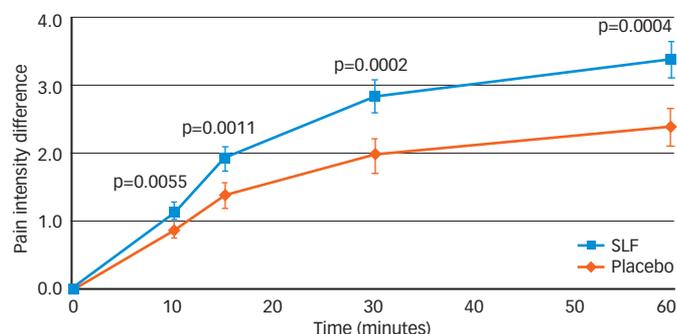
SLF is composed of micronised fentanyl citrate adhered to water-soluble carrier particles (mannitol) in an ordered mixture. The formulation is presented as a small tablet that, when placed under the tongue, rapidly disintegrates (usually within 10–15 seconds). The

**Figure 4: Mean Fentanyl Plasma Concentration Following Administration of Sublingual Fentanyl Citrate in Cancer Patients**



SLF = sublingual fentanyl citrate.  
Source: Lennernäs et al., 2004.<sup>14</sup>

**Figure 5: Mean Pain Intensity Difference from Baseline in Dose-titrated Sublingual Fentanyl Citrate and Placebo**



SLF = sublingual fentanyl citrate.  
Source: Rauck et al., 2009.<sup>15</sup>

**Table 1: Titration Schedule for Sublingual Fentanyl Citrate**

Strength (µg) of First Sublingual Tablet per Episode of Breakthrough Pain	Strength (µg) of Supplemental (Second) Sublingual Tablet to Be Taken 15–30 Minutes After First Tablet, If Required
100	100
200	100
300	100
400	200
600	200
800	–

Source: Abstral SPC.<sup>17</sup>

carrier particles adhere to the sublingual mucosa through a bioadhesive component (croscarmellose sodium) (see Figure 3).<sup>11</sup> The fentanyl dissolves completely and the bioadhesive agent maximises the surface area for absorption, facilitates rapid transit of fentanyl through the sublingual mucosa and prevents the drug from being swallowed.

This site-specific mechanism is designed to take advantage of the specific conditions of the sublingual environment using a technology designed to deliver the fentanyl effectively even in patients with dry mouth where saliva production is reduced, which may be a significant benefit in patients with mucositis. Furthermore, patients unable to tolerate oral administration due to nausea or dysphagia may also benefit.

## Clinical Development of Sublingual Fentanyl

The pharmacokinetic and efficacy profile of SLF has been comprehensively characterised through an extensive programme of phase I, II and III trials.

### Pharmacokinetics in Healthy Volunteers

The pharmacokinetic profile of SLF has been assessed in healthy volunteers in three phase I studies comprising a total of 85 subjects.<sup>12,13</sup> The results demonstrated that fentanyl was rapidly absorbed from the oral mucosa, being quantifiable in plasma within 4.8–15 minutes of administration and reaching a maximal plasma concentration after 30–75 minutes. Dose proportionality was observed in key pharmacokinetic parameters, which were not significantly affected by ethnicity, gender or single or multiple dosing.

### Pharmacokinetics in Opioid-tolerant Cancer Patients

The pharmacokinetic profile of SLF has been assessed in a phase I trial of 11 opioid-tolerant cancer patients.<sup>14</sup> Using a randomised, multicentre, double-blind, single-dose, two-period cross-over study followed by a third open-label period design, the findings were as expected from the findings observed in healthy volunteers. Fentanyl was rapidly absorbed from the oral mucosa, with the drug first quantifiable in the plasma eight to 11 minutes post-dose and reaching a maximum concentration within one hour. Three doses of SLF were tested (100, 200 and 400µg) and the measurements all showed dose proportionality, with the greatest peak plasma concentration being observed for the 400µg dose (see Figure 4).

### Efficacy

Adult patients with breakthrough pain using ATC opioids for background pain were enrolled into a phase III multicentre, multiple-dose study comprising a two-week open-label dose-titration phase followed by a two-week randomised, double-blind, placebo-controlled efficacy phase in which they received 10 treatment doses (seven SLF and three placebo) in a random order.<sup>15</sup> The primary end-point was the sum of pain intensity difference (SPID) from baseline to 30 minutes post-treatment. Secondary end-points included PID at 10, 15, 30 and 60 minutes. Efficacy was followed by an open-label safety period of up to 12 months.

During the efficacy phase, the mean SPID at 30 minutes was 49.3 and 35.23 for SLF and placebo, respectively (n=61; p=0.0004). SLF gave rise to significantly improved PID relative to placebo from 10 minutes post-dose through to the 60-minute time-point (p<0.0055) (see Figure 5). The presence or absence of a relationship between the successful SLF dose and ATC opioid dose was not demonstrated; titration is therefore recommended.

### Safety and Tolerability

The safety and tolerability of SLF were assessed in all of the aforementioned studies. The long-term tolerability of SLF was further examined in a multicentre multiple-dose study comprising a two-week open-label dose-titration phase followed by a 12-month open-label safety phase in adult patients. The data currently available relate to serious adverse effects and indicate that SLF is well tolerated in adult patients using ATC opioids for background pain. The adverse effects were those commonly seen with fentanyl administration and included nausea, dizziness and vomiting; most were mild to moderate in severity.<sup>16</sup> Adverse effects observed during

long-term assessment were reflective of the underlying disease and physical condition of the patients.

## Clinical Application of Sublingual Fentanyl Citrate

SLF should be administered only to adult patients already taking at least 60mg oral morphine per day or an equivalent alternative ATC opioid for one week or longer.<sup>17</sup> SLF should be administered directly under the tongue at the deepest part and should not be swallowed, but rather allowed to completely dissolve in the sublingual cavity without chewing or sucking. Patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved. Patients with dry mouth are advised to moisten the buccal mucosa with water before taking SLF.

## Titration

All patients must start therapy with a single 100µg sublingual tablet. If adequate analgesia is not obtained within 15–30 minutes of administration of a single sublingual tablet, a second 100µg sublingual tablet may be administered. If inadequate pain relief is obtained with 2x100µg sublingual tablets, an increase in dose to the next highest available strength for the next episode of breakthrough pain should be considered. Dose escalation should continue in a stepwise manner until adequate analgesia is achieved (see *Table 1*). This titration should follow the course of administration of a single sublingual tablet, with administration of a supplemental second sublingual tablet after 15–30 minutes if inadequate pain relief is obtained. The dose strength for the supplemental sublingual tablet should be increased from 100 to 200µg at doses of 400µg and above. No more than two sublingual tablets should be administered for a single episode of breakthrough pain during this titration phase. If adequate analgesia is achieved at the higher dose but side effects are considered unacceptable, an intermediate dose may be administered. Doses >800µg have not been evaluated in clinical studies.

## Dose Re-adjustment

If the response (analgesia or adverse reactions) to the titrated SLF dose markedly changes, an adjustment of dose may be necessary to ensure that an optimal dose is maintained. If more than four episodes of breakthrough pain are experienced per day, the dose of the ATC opioid used for background pain should be reviewed. If the ATC opioid is changed, the SLF dose should be reviewed and, if

necessary, re-titrated to ensure the patient remains on an optimal dose. This should be monitored by a health professional.

For patients no longer requiring any opioid therapy, the SLF dose should be taken into consideration before a gradual downward titration of opioids to minimise possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, SLF therapy can usually be discontinued immediately.

## Contraindications

SLF is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients, in opioid-naïve patients because of the risk of life-threatening respiratory depression and in patients with severe respiratory depression or severe obstructive lung conditions.

## Summary

Breakthrough pain has been shown to occur commonly in patients with cancer and is often severe, of sudden onset and short duration, or excruciating and short-lasting, making management difficult. The ideal treatment for breakthrough pain should match the clinical and dynamic profile of the pain. SLF is indicated for the management of breakthrough pain in patients with cancer who are already receiving opioid therapy for their background cancer pain.

The pharmacokinetic, efficacy, tolerability and safety profile of SLF suggests that it has a valuable role to play in the symptomatic pharmacological management of breakthrough pain. The effective dose of SLF cannot be predicted from previous ATC or rescue medication; therefore, titration is required to determine the effective dose according to the needs of the individual patient. ■



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