Therapeutic Reviews

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Fentanyl (transmucosal) *AHFS 28:08.08*

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This is a rapidly changing area, with six transmucosal fentanyl products available and more expected. Relative to PO opioids, the licensed products are expensive (ranging between $17–120/episode). They are more effective than placebo, but direct comparison with PO morphine, or each other, is limited.
Careful patient selection, training, titration and monitoring are required to ensure optimum use. They are *not* interchangeable. Because of safety concerns, all distributors, pharmacies and prescribers (to outpatients) are required by the FDA to enroll in a Risk Evaluation and Mitigation Strategy (REMS), with a shared scheme covering all transmucosal immediate-release fentanyl products (TIRF REMS) now available.

Class: Strong opioid analgesic.

Indications: Breakthrough (episodic) cancer pain in patients on regular strong opioids. The use of fentanyl injection SL or nasally is off-label.

Contraindications: Patients taking <60 mg morphine PO or equivalent/24 h, acute non-cancer pain (e.g., postoperative pain, migraine).

Pharmacology

Fentanyl (*like* morphine) is a strong μ-opioid receptor agonist. It has a relatively low molecular weight and (*unlike* morphine) is lipophilic, which makes it suitable for transmucosal administration. Multiple formulations are now licensed for the treatment of breakthrough (episodic) cancer pain, including a sublingual tablet (Abstral®), a lozenge (Actiq®), a buccal tablet (Fentora®), a buccal film (Onsolis®) and nasal sprays

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(Lazenda® and Instanyl®). Availability of the formulations varies by country and Instanyl® is not available in the U.S. A SL spray (Subsys®) is the latest to be approved, but, at the time of writing, published data are limited.

Breakthrough cancer pain generally has a relatively rapid onset and short duration, e.g. 20–30 min, but ranges from 1 min to 2–3 h.[1] By comparison, PO opioids such as morphine, on average, take about 30–40 min to achieve meaningful pain relief and have a longer duration of effect (3–6 h).[2] Thus, transmucosal fentanyl products aim to provide rapid onset pain relief that better matches the time course of a typical breakthrough pain.

The transmucosal formulations range from an aqueous solution of fentanyl (Instanyl®, Subsys®) to combinations with bio-adhesive substances, e.g., croscarmellose (Abstral®), pectin (Lazanda®) or cellulose-based polymers (Onsolis®). The pharmacokinetic characteristics of the products vary and they are *not* interchangeable (Table 1 and 2). Fentanyl is readily absorbed transmucosally and the bio-adhesive substances tend to *slow* its rate of absorption. Various justifications are given for the novel delivery systems, e.g., to aid mucosal adherence or to attenuate the peak plasma concentration. The fact that a novel delivery system can be patented is also relevant.

With the buccal/SL products, the amount of fentanyl absorbed directly across the mucosa or swallowed varies with formulation and route of administration. About two-thirds of any swallowed fentanyl will be eliminated by intestinal or hepatic first-pass metabolism. Nonetheless, significant amounts of swallowed fentanyl are absorbed, e.g., about 25%, 20% and 15% of the systemically available Actiq®, Onsolis® and Fentora®, respectively, is via GI absorption.[6,8,15] The effects of the GI absorption on the plasma concentration of fentanyl include producing a 'double peak,' maintaining high levels for longer (e.g., >2 h) and contributing to the wide range in T_{max}.[5]

The rate and degree of absorption of fentanyl from the nasal cavity is dependent on mucosal perfusion. Vasoconstrictive nasal decongestants, e.g., oxymetazoline, double the time to maximum plasma concentration and halve the maximum plasma concentration of a dose of nasal fentanyl. Thus, the concurrent use of vasoconstrictive nasal decongestants with Instanyl® or Lazanda® should be avoided.

Once absorbed, fentanyl is rapidly distributed to the best perfused tissues, i.e., brain, heart, lungs, and then to fat, muscle and other tissues. Subsequently, fentanyl is redistributed between the deep tissue compartment and plasma. This pattern of rapid distribution, followed by a slower redistribution explains why fentanyl has a relatively short duration of action despite a long half-life (Tables 1 and 2). However, with repeat administration, saturation of the deep tissue compartment can occur, resulting in higher peak plasma concentrations of fentanyl and a more prolonged effect.

Up to 85% of fentanyl is protein bound, mainly to α_1-acid glycoprotein, but also to albumin and lipoproteins. Elimination mainly involves biotransformation in the liver by CYP3A4 to inactive norfentanyl, which is excreted in the urine. Less than 7% is excreted unchanged. The product information (PI) provided with all of the transmucosal fentanyl products advises caution in their use in patients with moderate–severe hepatic or renal impairment, but this is based on limited data that suggest a reduced clearance of fentanyl, e.g., via alterations in metabolic clearance and plasma protein binding.

Pharmacokinetic studies of repeat/chronic dosing of the transmucosal products are limited. Repeating three single doses of Onsolis® at 1 h intervals results in a maximum plasma concentration three times higher than after a single dose.[16] Similarly, repeating a dose of Lazanda® after an interval of 1 or 2 h significantly increases the maximum plasma concentration, but not when given 4 h apart.[4] Accumulation of fentanyl can occur with regular use; when Fentora® 400microgram is given q6h, steady state is reached after about 5 days, and the maximum plasma concentration becomes double that of the initial dose.[17] Thus, even when an effective and tolerable dose is identified through titration, with subsequent regular use, accumulation and undesirable effects could occur.

Generally, patients recruited to the sponsor-supported studies for the fentanyl transmucosal products were relatively young (mean age 50–60 years), had a good performance status (ECOG PS 0–2), no clinically relevant renal or hepatic impairment, and were taking regular scheduled doses of an opioid equivalent to 160–280 mg morphine PO/24 h. Additional caution is required when giving these products to patients with characteristics that differ from this group, particularly those who are elderly.

Table 1
Selected Characteristics and Pharmacokinetic Data for *Oromucosal* Fentanyl Products[a,b]

	Abstral®	Actiq®[c]	Fentora®[d]	Onsolis®	*Subsys*®
Formulation	SL tablet	Buccal lozenge	Buccal/SL tablet	Buccal film	SL spray
Dose range and presentation	100, 200, 300, 400, 600, 800 microgram Different shapes and color coded, in pack of 12 or 32 (not 600 or 800 microgram)	200, 400, 600, 800, 1200, 1,600microgram On a stick, marked with dose, color coded, in pack of 30	100, 200, 400, 600, 800 microgram 100 smaller in size; embossed 1, 2, etc., in pack of 28	200, 400, 600, 800, 1,200 microgram Size increases with dose; marked with 2, 4, etc., color coded, in pack of 30	100, 200, 400, 600, 800, 1,200, 1,600microgram Single dose, color coded, in pack of 6, 14 or 28
Maximum dose/episode	800microgram	1,600microgram	800microgram	1,200microgram	1,600microgram
Maximum frequency of use	Maximum = 4 episodes/ 24 h, ideally ≥4 h apart (see Dose and Use)	Maximum = 4 episodes/ 24 h, ≥4 h apart	Maximum = 4 episodes/ 24 h, ≥4 h apart	Maximum = 4 episodes/ 24 h, ideally ≥4 h apart (see Dose and Use)	Maximum = 4 episodes/ 24 h, ≥4 h apart
Cost per episode [range]	$17–48	$20–66	$25–73	$26–74	$23–118
Time to dissolution	<2 min	Applied over 15 min	Buccal 14–25 min; SL quicker	15–30 min	N/A
Onset of action[e]	10 min	15 min	10 min	15 min	10 min
Time to peak plasma concentration, median (range)	30–60 min (15–240)	Across dose range 90 min (30–480)[3,4]	Pooled data 53 min (20–240)[5]	60–180 min (45–240) Longer with highest dose, and when 800 microgram administered as 4 200microgram films rather than single film (150 vs. 90 min)[6,7]	40–75 min (5–240) for 100–800microgram
Plasma half-life	Mean 5–14 h	Median 18 h (7–49) 800microgram[3]	Median 12 h (2–44), pooled data[5]	Mean 8–14 h, longer with higher doses[7]	Mean 5–12 h for 100–800microgram, longer with higher doses
Duration of action	≥1 h	≥1 h (≤3.5 h reported with higher doses)[8]	≥2 h	≥1 h	≥1 h
Bioavailability	70% (estimated)	50% (25% transmucosal, 25% PO)[8]	65% (50% transmucosal, 15% PO)	70% (50% transmucosal, 20% PO)[6]	75% (% transmucosal vs. PO not available)
Comments		Requires continual movement around the mouth; less effective if finished <15 min as more is swallowed	Absorption not affected by mild (grade 1) mucositis[9]	Absorption not affected by mild (grade 1) mucositis or by heat (e.g., a hot drink)[10,11]	Absorption increased in mild (grade 1) mucositis; monitor use carefully

[a]The source (i.e., healthy volunteers vs. patients) and quality (e.g., small number of subjects, whole dose range not studied, use of massage over buccal tablet) of the data varies widely.
[b]Data based on venous blood sampling; with arterial sampling, a higher maximum concentration is achieved about 15 min quicker.[12]
[c]A generic formulation of Actiq is available, which costs less.
[d]Pharmacokinetics are similar for either buccal or SL placement.
[e]Earliest *statistically significant* difference between fentanyl product and placebo in mean pain intensity difference; a *clinically meaningful* difference has been variably defined and generally takes longer (see text).

Table 2
Selected Characteristics and Pharmacokinetic Data for *Intranasal* Fentanyl Products[a]

	Instanyl® (not U.S.)	Lazanda®
Formulation	Nasal spray	Nasal spray
Dose range and presentation	50, 100, 200microgram/spray (100microL) 1 dose repeated once after 10 min p.r.n.; 10 and 20 dose bottles, color coded in pack of 1; also single-dose sprays in pack of 6	100, 200, 400 and 800microgram; given as 1 or 2 doses of 100 or 400microgram/spray (100microL); 8 dose bottles, color coded, in pack of 1 or 4
Maximum dose/episode	400microgram	800microgram
Maximum frequency of use	Maximum 4 episodes/24 h, ≥4 h apart	Maximum 4 episodes/24 h, ideally ≥4 h apart (see Dose and use)
Cost per episode [range]	N/A	$42–120
Time to dissolution	N/A	N/A
Onset of action[b]	5 min	10 min
Time to peak plasma concentration, median (range)	Across dose range 12–15 min (6–90 min)[13]	Across dose range 15–21 min (5–180 min)[4]
Plasma half-life	Median 19 h (8–30); 200microgram, 2 doses 10 min apart[14]	Mean 15–25 h
Duration of action	≥1 h	≥1 h
Bioavailability	90%	No data
Comments	Non-preserved solution, pH 6.6, osmolality ~0.9% saline	Preserved solution containing pectin, adjusted for pH and osmolality. Cmax is about 1/3 of that of Instanyl. Audible click denotes dose administered; visual priming guide and dose counter, end-of-use lock

[a]The source (i.e., healthy volunteers vs. patients) and quality (e.g., small number of subjects, whole dose range not studied) of the data varies widely.
[b]Earliest *statistically significant* difference between fentanyl product and placebo in mean pain intensity difference; a *clinically meaningful* difference has been variably defined and can take longer (see text).

A sober critique of the published papers also is required for various reasons, including:

- they are studies sponsored by the manufacturer, which raises concerns about the potential for bias
- although similar methods of evaluation are used across studies, the criteria used to define a response vary, making direct comparison difficult (see below)
- some approaches undertaken in the studies do not reflect recommended clinical practice, e.g.:
  - ➢ only single doses of Abstral® were used for titration and maintenance in the study on which its safety data is based, with the effective dose confirmed over several consecutive episodes; by comparison, in the PI, a second dose is permitted during titration, with no mention of confirmation of the effective dose[18]
  - ➢ Fentora® tablet remnants were 'massaged' after 10–15 min in the pharmacokinetic and some efficacy studies, potentially artificially enhancing absorption and efficacy data[19]
  - ➢ patients who had already used Instanyl® were enrolled into an efficacy study, artificially enhancing the proportion achieving successful titration (>90% vs. more usual 60–70%)[14]
  - ➢ the PI for Lazanda® and Onsolis® recommend a minimum gap of 2 h between doses, but 4 h was used in studies[20–22]
  - ➢ in some instances the regulatory authorities expressed concerns about the amount and/or the quality of the data, e.g. Abstral® pharmacokinetic data, Instanyl® safety reporting.[14,23]

For speed of onset of analgesia, generally what is promoted is the earliest *statistically significant* difference in pain intensity between the fentanyl product and placebo (generally 5–15 min). Although some patients report a reduction in pain intensity that is considered *clinically meaningful* by this time, this generally takes longer for most products. Reliable comparison of the different products is difficult because the definition and calculation of clinically meaningful change varies, e.g., reduction in pain intensity score from baseline of ≥2/10 or 30–33%, by episode (at least one or all) or by patient. Further, applying different criteria to the same data can produce different times, e.g., for Lazanda®, half of the patients experience a reduction in pain intensity score of ≥2 by 15 min, but a ≥33% reduction takes 30 min.[4,20] (Note: it has been suggested that a ≥50% improvement in pain intensity is required to be of *substantial* clinical importance.[24]) However, data suggest that for half of the episodes, an improvement in pain intensity of at least moderate

clinical importance appears by about 10 min (Instanyl® [25]), 15 min (Lazanda® [20]) or 30 min (Abstral®,[26] Actiq®,[27] Fentora®,[28] Onsolis®[22]). Even so, in up to a quarter of episodes, an alternative rescue analgesic is needed because of an inadequate response to the fentanyl product. Clinicians must provide careful explanation to ensure the patient uses both rescue analgesics correctly.

Comparative data, either between products or with PO analgesics, are limited (Box A). Generally, the transmucosal products perform statistically significantly better than the immediate-release PO formulations tested, but the absolute differences in outcomes are relatively small, making their clinical relevance uncertain (Box A).

Box A. Active comparator studies of transmucosal fentanyl products

Actiq® vs. PO morphine tablets[27]

Actiq®, titrated to an effective dose, has been compared with morphine *tablets* (previously identified effective dose, encapsulated to maintain blinding) in a double-blind, double-dummy, multiple cross-over study. For the primary and secondary outcomes, Actiq® was statistically superior to PO morphine tablets. However, the differences were small and their clinical relevance uncertain.

For example, for Actiq® vs. PO morphine tablets, the proportion of episodes after 15 min with clinically meaningful pain relief (defined as a ≥33% reduction in pain intensity) was 42 vs. 32%. Nonetheless, >90% of patients chose to continue with Actiq®.

Fentora® vs. PO oxycodone tablets[29]

Fentora® titrated to an effective dose, has been compared to oxycodone *tablets* (titrated to an effective dose and encapsulated to maintain blinding) in a double-blind, double-dummy, cross-over study in opioid-tolerant patients with non-cancer breakthrough pain. For the primary and most secondary outcomes, Fentora® was statistically superior to PO oxycodone tablets. However, the differences were small and their clinical relevance uncertain.

For example, for Fentora® vs. PO oxycodone tablets:

- mean (SD) pain intensity difference at 15 min (primary outcome) was 0.8 (1.1) vs. 0.6 (0.9)
- % of episodes with a reduction in pain intensity of ≥33% was 13 vs. 9% (15 min) and 41 vs. 32% (30 min); for a reduction ≥50%, it was 6 vs. 4% (15 min) and 21 vs. 16% (30 min)
- patients rated the overall medication performance as "good" to "excellent" in 41 vs. 26% of episodes at 30 min and 79 vs. 71% at 60 min.

Lazanda® vs. PO morphine tablets[30,31]

Lazanda®, titrated to an effective dose, has been compared with encapsulated morphine *tablets* (one-sixth of the total daily dose, or previously identified effective dose) in a double-blind, double-dummy, multiple cross-over study. For the primary and most secondary outcomes, Lazanda® was statistically superior to PO morphine tablets. However, the differences were small and their clinical relevance uncertain.

For example, for Lazanda® vs. PO morphine tablets:

- mean (SD) pain intensity difference at 15 min (primary outcome) was 3.0 (0.2) vs. 2.7 (0.2)
- % of episodes with clinically meaningful pain relief (defined as a ≥2 reduction in pain intensity) was 25 vs. 23% (5 min); 52 vs. 45% (10 min) and 76 vs. 69% (15 min).

Instanyl® vs. Actiq® [14,32]

Instanyl® and Actiq® (both titrated to an effective dose) have been compared in an open label RCT. The primary outcome was time to meaningful pain relief, measured by stop-watch. The fastest time to meaningful pain relief was significantly more likely with Instanyl® than Actiq®, with a median difference of 5 min (11 vs. 16 min, respectively). A second dose of Instanyl® or Actiq® was required in about 60% and 30% of episodes, respectively. For Instanyl® this was permitted 10 min after the first dose, and for Actiq® 15 min after fully consuming the first dose, i.e., at least 30 min after starting the first dose. Usual rescue analgesia was required in 5–8% of episodes. Patients found the administration of Instanyl® easier and overall preferred Instanyl® (75%) to Actiq® (25%).

Given the mismatch between the time-action relationship of PO morphine and the typical time course of a breakthrough pain, it is interesting to observe how well PO morphine performs in these studies. This is particularly so considering that, unlike the fentanyl product, the PO morphine dose was not optimized in a titration phase and also was given in tablet form. To fully determine the relative advantage of the transmucosal products over PO morphine in relation to speed of onset of action, morphine *solution* is the more appropriate comparator than *tablets*, because it is absorbed and acts more quickly. For example, studies have reported a median (range) T_{max} of 60 min (20–90) vs. 125 min (40–240) and mean time to meaningful pain relief of about 15 min vs. 30 min for morphine solution vs. tablets, respectively.[33,34]

The lack of comparative data among the transmucosal products prevents conclusions about the best to use. However, the practical aspects of using some of the products have been compared in a patient satisfaction survey.[35] Following instruction, 30 patients were asked to use a single *placebo* version of Abstral®, Fentora® and Instanyl® and to rate factors such as ease of access from packaging, ease of administration and palatability; they also rated their current rescue analgesic (generally PO morphine or oxycodone) similarly. They were asked to indicate if they would be prepared to use the transmucosal product and, if so, which they felt was the best and why. Several themes emerged:

- *ease of access:* the fentanyl products were generally more difficult to access than usual rescue analgesia, particularly the child-proof container for Instanyl®
- *ease of use:* Abstral® and the usual rescue analgesia were equal best
- *palatability:* Abstral® was rated best
- *patients willing to use:* Abstral® (90%) vs. Fentora® and Instanyl® (about 60% each); three patients would not use any (did not like the product or could not open the packaging)
- which is best and why?:
  - ➢ Abstral® (~70%); easy to access and use, dissolved quickly
  - ➢ Instanyl® (~20%); quick to use (once you get into package), route familiar
  - ➢ Fentora® (~10%); liked sensation in the mouth
  - ➢ one could not choose between Abstral® and Fentora®.

The use of placebos means that overall satisfaction with the products could not be compared. Nonetheless, taking these practical issues and other factors into account, the *Palliative Care Formulary* suggests the following in patients with cancer taking regular strong opioids and experiencing cancer-related breakthrough pain:

- use immediate-release PO strong opioids first-line and titrate accordingly (include a trial of a PO solution if tablets not adequate); only when inadequate with regard to speed of onset of action or prolonged undesirable effects should the transmucosal products be considered
- a patient's circumstances should be considered carefully to ensure they fulfill the necessary requirements for use of a transmucosal product, e.g., current opioid dose, ability to access, use, store and dispose of the product reliably, etc. (see Dose and Use)
- decide which route and product is the most appropriate, i.e.:
  - ➢ *nasal:* generally works quicker and shorter lasting (less PO absorption) than the SL/buccal route; Lazanda® works slightly slower than Instanyl®, but has a safer, accountable delivery system, and is cheaper
  - ➢ *SL/buccal:* there is little to choose from in terms of efficacy; Abstral® dissolves the quickest, making it the most convenient to use, and is cheaper. Onsolis® is less likely to cause dental caries and mucosal irritation compared to Actiq® and Fentora®, respectively.

There may be other more specific reasons that guide choice of route, e.g., patient preference, presence of severe dry mouth or mucositis (use nasal), or frequent nose bleeds (use SL/buccal).

U.K. Medicine advisory boards (e.g., Scottish Medicines Consortium, All Wales Medicines Strategy Group) also recommend restricting the use of transmucosal fentanyl products to patients unsuitable for other short-acting opioids, e.g., PO morphine.

As a cheaper alternative to the licensed transmucosal fentanyl products, some palliative care services use the parenteral formulation of various fentanils for SL administration, e.g., fentanyl (50microgram/mL), sufentanil (50microgram/mL) and alfentanil (500microgram/mL and 5 mg/mL).[36–38] Onset of analgesic effect may be broadly similar (5–10 min) but duration of effect is likely to differ

(fentanyl>sufentanil>alfentanil). Several small doses can be given until pain relief is obtained. Using a 1 mL graduated oral syringe:

- start with fentanyl 25−50microgram (0.5−1 mL of 50microgram/mL)
- if necessary, increase to 50−100microgram; many patients do not need more than this
- doses >100microgram are impractical because 2 mL is the maximum volume that can be reliably kept in the mouth for transmucosal absorption.[37]

Drawing up the correct amount of the parenteral formulation into a syringe is inconvenient, but this can be overcome by the use of a spray bottle.[38,39]

The 50microgram/mL fentanyl solution also has been administered as a nasal spray. In adults this approach is limited by the large dose volume. However, it has provided effective analgesia in children 1−18 years old presenting to the emergency department with acute moderate−severe pain.[40−42] A 1 mL syringe attached to a mucosal atomizer device permits the appropriate amount of fentanyl to be converted into a spray. The initial dose is generally 1−2microgram/kg, administered in divided doses to a maximum of 1 mL in each nostril, with some centers permitting a second dose of 0.5microgram/kg after 10 min if required.[41] Higher concentration fentanyl solutions up to 300microgram/mL also have been used. However, compared to the standard solution, they are less readily available, more expensive and, at least in children <50 kg, no more effective.[42,43]

Cautions

All companies provide additional information for prescribers, pharmacists and patients; these include checklists to ensure proper patient selection and education around use, signs of opioid overdose, safe storage and disposal (see also the Transmucosal Immediate-Release Fentanyl Risk Evaluation and Mitigation Strategy in Dose and Use). Store out of reach of children (accidental deaths have occurred).

In 2007, after reports of serious overdoses and deaths, the FDA issued a safety warning about the use of Fentora®. Factors that contributed to the adverse drug events included improper:

- patient selection, e.g., non-opioid tolerant, acute (non-cancer) pain
- dosing, e.g., wrong dose prescribed, exceeding recommended maximum use
- product substitution, e.g., microgram for microgram switch from Actiq® to Fentora®

Thus, these products need to be used correctly, specifically:

- do *not* use in opioid naïve (non-tolerant) patients, including those who only take strong opioids p.r.n.
- they are contraindicated in the management of acute pain, including postoperative, and headache/migraine
- they are not interchangeable; do *not* convert patients on a microgram per microgram basis from one to another; it is necessary to titrate the new formulation
- when dispensing, do *not* substitute one product for another.

These safety concerns, together with the risk of misuse, are highlighted in a warning black box in the PI for all licensed transmucosal fentanyl products.

Use with caution in patients with COPD or other medical conditions predisposing them to respiratory depression (e.g., myasthenia gravis) or susceptible to the intracranial effects of hypercapnia (e.g., those with raised intracranial pressure). Also if bradyarrhythmia, elderly, cachectic, debilitated, moderate−severe hepatic or renal impairment, hypovolemia, hypotension; and if a history or high risk of abuse or diversion.

Mouth wounds, mucositis (may enhance absorption); nasal vasoconstrictive decongestants (reduce the effect of Lazanda®), other nasal medications (unknown effect; U.K. SPC advises avoiding within 15 min of a dose of Lazanda®), epistaxis.

Actiq® contains 2 g of sugars; inform diabetic patients, also risk of tooth decay (uncommon).

Drug Interactions

Fentanyl is metabolized by CYP3A4. Thus, fentanyl plasma concentrations may be increased by CYP3A4 inhibitors such as azole antifungals (e.g., fluconazole, ketoconzole, itraconazole), macrolide antibiotics (e.g., erythromycin, clarithromycin), protease inhibitors (e.g., ritonavir, nelfinavir), aprepitant, cimetidine, diltiazem and verapamil.[44]

In contrast, concentrations are decreased by potent CYP3A4 inducers (e.g., carbamazepine, phenytoin, phenobarbitone, rifampicin) and this may lead to a loss of analgesia.[44–48]

Fentanyl is best avoided in patients who have used a MAOI within the past 2 weeks. Although they have been used safely together, serotonin toxicity (sometimes fatal) has occurred.[44]

Undesirable Effects

Typical of any strong opioid. Patients should be counseled accordingly, including effects on ability to drive or operate machinery.

Very common (>1/10): drowsiness, dizziness, headache, confusion, nausea, vomiting, sweating.

Topical effects: less common and formulation-dependent, but include: oral and nasal discomfort, inflammation or ulceration, rhinorrhea, epistaxis, sore throat, dysguesia, dental caries with Actiq® (uncommon).

Dose and Use

All distributors, pharmacies (via an authorized pharmacist) and prescribers (to outpatients) are required by the FDA to enroll in a Risk Evaluation and Mitigation Strategy (REMS); a shared scheme that covers all transmucosal fentanyl products (TIRF REMS) is now available.[49] Requirements include prescribers undertaking a training package and knowledge assessment every two years. Patients must receive verbal and written instruction on the correct use of the drug and complete a patient-prescriber agreement form.

Prescribers of transmucosal fentanyl products should:

- be experienced in the management of opioid-therapy in cancer patients
- limit use to opioid-tolerant patients who can adhere to the instructions regarding indication, administration, storage and returns
- provide ongoing supervision
- keep in mind the potential for fentanyl to be misused[50–53]
- understand that the formulations are *not* bioequivalent and thus *not* interchangeable; when switching products, re-titration from the lowest available dose is required.

Transmucosal fentanyl products should be used only in adults on a regular strong opioid for chronic cancer pain for ≥1 week:

- morphine 60 mg/24 h PO
- fentanyl 25microgram/h transdermal patch
- hydromorphone 8 mg/24 h PO
- oxycodone 30 mg/24 h PO
- oxymorphone 25 mg/24 h PO
- an equivalent dose of another opioid.

Individual titration is required because a successful dose cannot be reliably predicted from the maintenance dose of opioid.[19,29,32,54–56] Careful monitoring is required during initial or subsequent titration; the complexity of the titration schedules varies between products (Box B–H). Even so, transmucosal fentanyl products are unsatisfactory in about 1/4–1/3 of patients, either because they fail to provide relief at the highest practical dose or cause unacceptable undesirable effects.

The optimal dose found during successful titration (Box B–H) can be used to treat up to 4 breakthrough pain episodes/24 h. The recommended minimum interval between treatments varies between products and even for the same product between countries, e.g., Lazanda®. The PI for Abstral®, Lazanda® and Onsolis® specify ≥2 h, and for the remaining products ≥4 h apart. However, applying the latter rule across all products would be reasonable because it was used by most studies and more frequent dosing than q4 h appears to increase the maximum plasma concentration achieved with the

subsequent dose of fentanyl.[4] Thus, an alternative p.r.n. analgesic, e.g., morphine PO, will be required to treat any additional, more frequent episodes. Further, in about 5–25% of episodes, the transmucosal products fail to provide adequate relief and an alternative analgesic is required.[21,56]

Box B. Abstral® dose and use

Follow the manufacturer's guidance on administration, titration, storage and disposal in the PI and Medication guide.

Abstral® is a SL tablet, placed in the deepest part under the tongue. The tablets must not be chewed or sucked and patients should not eat or drink until they have dissolved. Those with a dry mouth may moisten it with water beforehand. The tablet generally dissolves quickly (<5 min), with the particles produced adhering to the oral mucosa from which the fentanyl is subsequently absorbed.

Evaluate each dose after 30 min and if successful, i.e., a *single* dose provides adequate analgesia with little or no undesirable effects, this is the maintenance dose. If unsuccessful, during titration, the same dose can be repeated *once*, and subsequently a higher dose used for the next episode. Note: supplemental doses are higher than those recommend in the U.K., which are given in parentheses:

- start with 100microgram, if unsuccessful, give an additional 100microgram dose
- for the next episode give 200microgram, if unsuccessful, give an additional 200microgram (U.K. 100microgram)
- for the next episode give 300microgram, if unsuccessful, give an additional 300microgram (U.K. 100microgram)
- for the next episode give 400microgram, if unsuccessful, give an additional 400microgram tablet (U.K. 200microgram)
- for the next episode give 600microgram, if unsuccessful, give an additional 600microgram tablet (U.K. 200microgram)
- for the next episode give 800microgram, the maximum dose.

Note: in the efficacy and safety study, only single doses of Abstral® were used for titration and maintenance, with the effective dose confirmed over several consecutive episodes.[18] During titration, multiples of the 100microgram or 200microgram tablets can be used, up to a maximum of 4 tablets.

More than two-thirds of patients find an effective and tolerable dose; about one-quarter require 800microgram.[57] However, because of inadequate relief after 30 min, an alternative rescue analgesic is needed in about 10% of episodes.[18]

A maximum of 4 breakthrough pain episodes/24 h can be treated. In studies, this had to be ≥2 h apart (each pain episode was limited to treatment with a single dose);[18,58] ≥ 4 h apart is the ideal (see text). Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and possible increase in the dose of the regular strong opioid. Subsequently, if a single dose of Abstral® fails to provide consistent relief, the dose should be further titrated as above.

Abstral® is generally well tolerated and remains effective. Use of a median dose of 600microgram treating a mean of 3 episodes/day for 5–6 months showed that:

- opioid-related undesirable effects (e.g., nausea) are common but not a major cause of discontinuation
- application site irritation rarely occurred
- about 75% of patients were satisfied or very satisfied with its use.[18,58]

Box C. Actiq® dose and use

Follow the manufacturer's guidance on administration, titration, storage and disposal in the PI and Medication guide.

Actiq® is a 'lozenge on a stick' containing fentanyl in a hard sweet matrix. In order to achieve maximum mucosal exposure to the fentanyl, the lozenge should be placed between the cheek and the gum and moved constantly up and down, and changed at intervals from one cheek to the other. It should not be chewed. The lozenge should be consumed completely over 15 min; quicker than this and more fentanyl is swallowed. Patients with xerostomia (dry mouth) may find it hard to consume it in this time period.[59] If necessary, moisten the mouth with water beforehand. Initially, prescribe 6 doses of one strength at a time:

- start with fentanyl 200microgram and consume over 15 min; drinking or eating is not permitted during administration
- wait 15 min; if there is inadequate analgesia, use a second 200microgram lozenge
- not more than two lozenges should be used for any one episode of pain
- continue with 200microgram for a further 2 episodes of pain, allowing a second lozenge when necessary
- if on review, the breakthrough (episodic) pain is not controlled satisfactorily with a single 200microgram dose, increase to 400microgram
- wait 15 min; use a second 400microgram lozenge if necessary
- continue this upward titration through the available dose strengths until a *single* dose provides adequate analgesia with little or no undesirable effects; this is the maintenance dose
- the maximum dose is 1,600microgram.

The lozenge should be removed from the mouth once the pain is relieved; partly consumed lozenges should be dissolved under hot running water and the handle discarded in a waste container out of reach of children.

About three-quarters of patients find an effective and tolerable dose. An alternative rescue analgesic is required in 5–15% of episodes (permitted if inadequate response 15 min after Actiq® dose fully consumed).

A maximum of 4 breakthrough pain episodes/24 h can be treated with at least 4 h between doses. Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and possible increase in the dose of the regular strong opioid. Subsequently, if a single dose of Actiq® fails to provide consistent relief, the dose should be further titrated as detailed above.

Actiq® is generally well tolerated and remains effective. Follow-up over a mean of about 3 months showed that:

- opioid-related undesirable effects are common (e.g., nausea) but not a major cause of discontinuation
- a single dose is effective in 85–90% of episodes
- about 1/2–3/4 of patients require a dose adjustment; mostly upwards, but sometimes downwards
- patient ratings of global medication performance remain the same (generally 'very good').[60,61]

Box D. Fentora® dose and use

Follow the manufacturer's guidance on administration, titration, storage and disposal in the PI and Medication guide.

Fentora® is a tablet that can be placed either buccally (between the cheek and gum near a molar tooth) or SL. Absorption is similar from both sites, but it dissolves quicker SL.[62] A dry mouth should be moistened with water beforehand. Mild mucositis (grade 1) does not affect absorption,[9] but avoid use in more severe grades because the impact on absorption has not been examined.

The tablets must not be chewed or sucked and patients should not eat or drink until they have dissolved. The time to dissolution is generally 15–25 min but can be longer. However, any tablet remnants should be swallowed after 30 min with a glass of water.

Prescribe only one dose strength at a time (100 or 200microgram during titration); up to 4 tablets can be used simultaneously. Evaluate each dose after 30 min and, if successful, this is the maintenance dose. If unsuccessful, during the titration phase, a maximum of one further dose can be given.

Evaluate each dose strength over 3–4 episodes; increase to the next higher strength if there is frequent need for a second dose. Note: in the UK each dose strength is evaluated over a single episode; some supplemental doses are lower and are given in parentheses:

- start with 100microgram, if unsuccessful, give an additional 100microgram dose
- if unsuccessful over several episodes, give 200microgram (2 × 100microgram tablets), if unsuccessful for that episode, give an additional 200microgram
- if unsuccessful over several episodes, give 400microgram (4 × 100microgram tablets), if unsuccessful for that episode, give an additional 400microgram (U.K. 200microgram)
- if unsuccessful over several episodes, give 600microgram (3 × 200microgram tablets), if unsuccessful for that episode, give an additional 600microgram (U.K. 200microgram)
- if unsuccessful over several episodes, give the maximum dose of 800microgram (4 × 200microgram tablets).

About two-thirds of patients find an effective and tolerable dose. Subsequently only a *single* dose of the appropriate strength tablet is used per episode. An alternative rescue analgesic is required in about 10–25% of episodes.

An initial dose of 100microgram should always be used *except* when converting patients from higher doses of Actiq® when initial doses of 200microgam (for those on 600 or 800microgram Actiq®) or 400microgram (for those on 1,200 or 1,600microgram Actiq®) can be used.

A maximum of 4 breakthrough pain episodes/24 h can be treated, with at least 4 h between doses. Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and possible increase in the dose of the regular strong opioid. Subsequently, if a single dose of Fentora® fails to provide consistent relief, the dose may require further titration as above.

Fentora® is generally well tolerated and remains effective. Follow-up over a mean of 6 months showed that:

- opioid-related undesirable effects are common (e.g., nausea) but not a major cause of discontinuation
- application site problems (e.g., pain, irritation, ulceration) are seen in 6% and lead to discontinuation in <2%

- 70% of patients continue on the same dose
- patient ratings of global medication performance remain the same (generally 'good').[63]

Although only licensed for up to 800microgram in breakthrough cancer pain, data exist for the use of Fentora® in:
- highly opioid-tolerant cancer patients (>700 mg oral morphine equivalent/24 h) in doses of 1,200–3,200microgram[64]
- opioid-tolerant patients with non-cancer breakthrough pain, e.g., degenerative back pain, complex regional pain syndrome[29,50,65–67]
- opioid-naïve patients with severe pain attending emergency departments with possible or definite fractures or dislocations (single dose of 100microgram).[68]

The use of Fentora® in non-cancer patients is controversial, and concerns exist around safety and the potential for misuse.[50–52]

Box E. Onsolis® dose and use

Follow the manufacturer's guidance on administration, titration, storage and disposal in the PI and Medication Guide.

Onsolis® is a soluble film that is placed on the lower gum below the level of the teeth. After removal from its package, Onsolis® should be used immediately to prevent it drying out. Before application, the cheek is wetted either with the tongue or by rinsing with water. Using a dry finger, the pink side of the film is held against the cheek for 5 seconds to ensure adherence to the mucosa. Subsequently, the film should not be touched or moved. Drinking is permitted after 5 min, but food should be avoided until the film has dissolved completely (generally 15–30 min). Most patients notice a taste, which is considered pleasant/acceptable by >90%.

Onsolis® must not be cut, torn, rubbed with the tongue, chewed or swallowed. Mild mucositis (grade 1) does not affect absorption,[10] but avoid use in more severe grades because the impact on absorption has not been examined.

Evaluate each dose after 30 min and, if successful, this is the maintenance dose. If ineffective, an alternative rescue analgesic can be given. Up to four 200microgram films may be applied, two on either side of the mouth, placed so as not to overlap:
- start with 200microgram
- if unsuccessful, for the next episode, give 400microgram (2 × 200microgram films)
- if unsuccessful, for the next episode, give 600microgram (3 × 200microgram films)
- if unsuccessful, for the next episode, give 800microgram (4 × 200microgram films)
- if unsuccessful, for the next episode, increase to the maximum dose of 1,200microgram (1 × 1,200microgram film).

About two-thirds of patients find an effective and tolerable dose. Subsequently only a *single* film of the appropriate strength is used per episode. An alternative rescue analgesic is required in about 10–30% of episodes.

A maximum of 4 breakthrough pain episodes/24 h can be treated. The PI recommends ≥2 h between doses, although ≥4 h was used in one of the studies,[22] and is the ideal (see text).

Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and possible increase in the dose of the regular strong opioid. Subsequently, if a single dose of Onsolis® fails to provide consistent relief, the dose may require further titration as above.

Onsolis® is generally well tolerated and remains effective. Follow-up over a mean of 4 months (in a study which permitted doses up to 2,400microgram) showed that:[69]

- opioid-related undesirable effects are common (e.g., nausea) but not a major cause of discontinuation
- application site problems (e.g., pain, irritation, ulceration) are seen in <3% but are generally mild and do not necessitate discontinuation
- about three-quarters of patients continue on the same dose
- patient ratings of global medication performance were 'good' to 'excellent' in 85% of episodes.

Box F. Subsys® dose and use

Follow the manufacturer's guidance on administration, titration, storage and disposal in the PI and Medication Guide.

Subsys® is a SL spray provided in single-dose units. To administer a dose, patients first swallow any saliva and then, holding the spray unit upright, the nozzle is placed in the mouth and aimed under the tongue, before being actuated. Most patients will notice a taste; they should retain the solution under the tongue for 30–60 seconds, not spit any out or rinse the mouth. Absorption is unaffected by the temperature or pH of drinks taken immediately before administration.

Mucositis increases absorption of fentanyl; use of Subsys® in mild mucositis (grade 1) is permitted with closer monitoring, but should generally be avoided in more severe grades. Subsys® contains alcohol and some patients with mucositis report a burning sensation after administration.

Prescribe only one dose strength at a time; packs of 6 are available for titration purposes. Evaluate each dose after 30 min; if successful, this is the maintenance dose. If unsuccessful, during the titration phase, a maximum of one further dose can be given.

Evaluate each dose strength over 3–4 episodes; increase to the next higher strength if there is frequent need for a second dose:

- start with 100microgram, if unsuccessful, give an additional 100microgram dose
- if unsuccessful over several episodes, give 200microgram (1 × 200microgram), if unsuccessful for that episode, give an additional 200microgram
- if unsuccessful over several episodes, give 400microgram (1 × 400microgram), if unsuccessful for that episode, give an additional 400microgram
- if unsuccessful over several episodes, give 600microgram (1 × 600microgram), if unsuccessful for that episode, give an additional 600microgram
- if unsuccessful over several episodes, give 800microgram (1 × 800microgram), if unsuccessful for that episode, give an additional 800microgram
- if unsuccessful over several episodes, give 1,200microgram (2 × 600microgram), if unsuccessful for that episode, give an additional 1,200microgram
- if unsuccessful over several episodes, give the maximum dose of 1,600microgram (2 × 800microgram).

About three-quarters of patients find an effective and tolerable dose. Subsequently only a *single* spray of the appropriate strength is used per episode, which can be supplied in packs of 14 or 28. An alternative rescue analgesic is required in about 10% of episodes.

A maximum of 4 breakthrough pain episodes/24 h can be treated, with at least 4 h between doses. Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and

possible increase in the dose of the regular strong opioid. Subsequently, if a single dose of Subsys® fails to provide consistent relief, the dose may require further titration as above.

Subsys® is generally well tolerated. Follow-up over a mean of 2 months showed that:
- opioid-related undesirable effects are common (e.g., nausea) but not a major cause of discontinuation
- application site problems (e.g., erythema, edema) are seen in 10% but are generally mild and do not necessitate discontinuation.[70]

Box G. Instanyl® dose and use (not U.S.)

Follow the guidance on priming, administration, storage and disposal in the Manufacturer's SPC, Physician and Pharmacist guides, Patient Brochure/Information Leaflet.

Instanyl® is a nasal spray. Not all patients feel the spray and they should be warned not to repeat the dose because of this. There is no dose counter.

Evaluate each dose after 10 min and if successful, this is the maintenance dose; if unsuccessful, a maximum of one further dose can be given.

Evaluate each dose strength over 3–4 episodes; increase to the next higher strength if there is frequent need for a second dose:
- start with 50microgram in one nostril, if unsuccessful give an additional 50microgram in the other nostril
- if unsuccessful over several episodes, give 100microgram in one nostril, if necessary give an additional 100microgram in the other nostril
- if unsuccessful over several episodes, give 200microgram in one nostril, if necessary give an additional 200microgram in the other nostril; this is the *maximum* dose.

About 2/3–3/4 of patients find an effective and tolerable dose. Although the aim is to use only one dose per episode, >50% require a second dose. An alternative rescue analgesic is required in about 15% of episodes; this is given after waiting ≥10 min after a dose of Instanyl®.

A maximum of 4 breakthrough pain episodes/24 h can be treated, with at least 4 h between doses (including any other rescue analgesic used). Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and possible increase in the dose of the regular strong opioid. The dose of Instanyl® may subsequently need to be re-titrated.

Instanyl® is generally well tolerated; opioid-related undesirable effects are common (e.g., nausea) but not a major cause of discontinuation.

The bottles should be stored upright in the child-resistant container for safety; if not used for >1 week, they need to be primed again by spraying a single dose in the air.

Box H. Lazanda® dose and use

Follow the guidance on priming, administration, storage and disposal in the manufacturer's PI and Medication guide.

Lazanda® is a nasal spray. Not all patients feel the spray, but there is an audible click when the dose is administered, and the dose counter advances by one. Advise patients not to blow their nose for 1 h after administration:

- start with 100microgram in one nostril
- if unsuccessful, for the next episode, give 200microgram (100microgram in each nostril)
- if unsuccessful, for the next episode, prescribe higher concentration formulation and give 400microgram in one nostril
- if unsuccessful, for the next episode, increase to the maximum dose of 800microgram (400microgram in each nostril).

Evaluate each dose after 30 min and, if ineffective, an alternative rescue analgesic can be given.

If any of the above doses are successful, this should be confirmed in the next episode. About three-quarters of patients find an effective and tolerable dose; an alternative rescue analgesic is needed in about 5–10% of episodes. Subsequently, if a previously effective dose fails to provide relief over several episodes, consider titration to a higher dose.

A maximum of 4 breakthrough pain episodes/24 h can be treated, with at least 4 h between doses (including any other rescue analgesic used). The PI recommends ≥2 h between doses, although ≥4 h was used in studies,[20,21] and is the ideal (see text). Regular daily use of breakthrough medication (traditionally ≥2/24 h) should prompt a review and a possible increase in the dose of the regular strong opioid. The dose of Lazanda ® may subsequently need to be re-titrated.

Lazanda® is generally well tolerated and remains effective. Follow-up over a mean of 4 months showed that:

- <3% of patients dropped out because of drug-related undesirable effects
- 90% continued on the same dose
- 90% were satisfied or very satisfied with its use.[20,21]

The bottles should be kept in the child-resistant container for safety, and disposed of 2 weeks after priming or if >5 days have elapsed since last use.

Supply

All preparations are fentanyl citrate and Schedule II controlled substances.

Buccal products

Abstral® (ProStrakan)

Tablet sublingual 100microgram, 1 tablet = $17; 200microgram, 1 tablet = $19; 300microgram, 1 tablet = $23; 400microgram, 1 tablet = $29; 600microgram, 1 tablet = $38; 800microgram, 1 tablet = $48.

Actiq® (Cephalon)

Lozenge buccal with oromucosal applicator 200microgram, 1 lozenge = $20; 400microgram, 1 lozenge = $25; 600microgram, 1 lozenge = $31; 800microgram, 1 lozenge = $36; 1,200microgram, 1 lozenge = $54; and 1,600microgram, 1 lozenge = $66.

Fentanyl citrate oral transmucosal lozenge (generic)
Lozenge buccal with oromucosal applicator 200microgram, 1 lozenge = $17; 400microgram, 1 lozenge = $20; 600microgram, 1 lozenge = $25; 800microgram, 1 lozenge = $30; 1,200microgram, 1 lozenge = $35; and 1,600microgram, 1 lozenge = $40.

Fentora® (Cephalon)
Tablet buccal 100microgram, 1 tablet = $25; 200microgram, 1 tablet = $31; 400microgram, 1 tablet = $46; 600microgram, 1 tablet = $59; 800microgram, 1 tablet = $73. The 300microgram tablet has recently been discontinued.

Onsolis® (Meda)
Soluble film buccal 200microgram, 1 film = $26; 400microgram, 1 film = $38; 600microgram, 1 film = $50; 800microgram, 1 film = $62; 1,200microgram, 1 film = $74.
Subsys® (Insys)

Sublingual spray 100microgram, 1 spray = $23; 200microgram, 1 spray = $29; 400microgram, 1 spray = $42; 600microgram, 1 spray = $54; 800microgram, 1 spray = $67; 1,200microgram (2 x 600microgram, in specific carton) = $92; 1,600microgram (2 x 800microgram, in specific carton) = $118.

Nasal spray
Lazanda® (Archimedes)
Nasal spray 100microgram/metered dose spray, 1 spray = $42; 400microgram/metered dose spray, 1 spray = $60; the dose required may consist of 1 or 2 sprays.

Injection
Sublimaze preservative-free® (Akorn)
Injection 50microgram/mL, 2 mL amp = $0.50, 30 mL amp = $11.

Note. In the U.K., Fentora®, Lazanda® and Onsolis® are known as Effentora®, Pecfent® and Breakyl®, respectively; for all of the transmucosal products, the price per dose is also the same, regardless of strength.

Abbreviations/Key

COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
ECOG PS	Eastern Cooperative Oncology Group performance status
FDA	Food and Drug Administration
GI	Gastro-intestinal
MAOI	Mono-amine oxidase inhibitor
PI	Package insert(s)
PO	Per os, by mouth
p.r.n.	Pro re nata, as required
q4h	Every 4 hours, etc.
SL	Sublingual
SPC	Summary of Product Characteristics (UK)
T_{max}	Time to maximum plasma concentration

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