PrescQIPP Community Interest Company

Immediate-release fentanyl

In England and Wales £36.1 million is spent annually on the prescribing of fentanyl preparations, of which £6.7 million is for immediate-release fentanyl (NHSBSA September to November 2020).

QIPP projects in this area are aimed at supporting prescribers in either reviewing the continued need for immediate-release fentanyl and deprescribing, or switching to a product with lower acquisition cost (for example the immediate-release morphine equivalent) if appropriate. This bulletin reviews the place in therapy of immediate-release fentanyl and offers guidance and support material for organisations considering reviewing immediate-release fentanyl prescribing as a QIPP project.

Recommendations

- In line with NICE guidance, offer oral immediate-release morphine for the first-line rescue medication for breakthrough pain in patients on maintenance oral morphine treatment.
- Do not initiate immediate-release fentanyl in primary care as first-line rescue medication for any new patient (a 'NICE Do Not Do' Recommendation).
- Deprescribe immediate-release fentanyl in all patients, if appropriate, and ensure the availability of relevant services to facilitate this change.
- Immediate-release fentanyl products are licensed only for the treatment of breakthrough pain in adults receiving opioid therapy for chronic cancer pain. They are not licensed for any other type of pain.
- Use outside of the licence (e.g. for non-cancer pain or for patients not taking at least 60mg of oral morphine daily or equivalent) has safety implications and should be reviewed.
- Immediate-release fentanyl preparations should be discontinued immediately if the patient no longer experiences breakthrough pain episodes.
- Patients receiving immediate-release fentanyl, who have not tried immediate-release morphine first-line, could be considered for a switch. There is no well-established method for converting between them, immediate-release morphine is usually dosed as a proportion of the background analgesia dose. Appropriate specialist input should be sought.
- In exceptional circumstances, immediate-release fentanyl may be considered for prescribing in primary care, (e.g. in breakthrough pain in adults when other short-acting opioids are unsuitable). This should be undertaken in a co-operation arrangement with a multi-disciplinary team and/or other healthcare professionals and be clearly documented in the patient's record.
- An individual's circumstances should be considered carefully to ensure they fulfil 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.
- Patients receiving the most costly immediate-release fentanyl products (Actiq® lozenges, Instanyl® nasal spray) who can't be switched to immediate-release morphine could be considered for a switch to a less costly immediate-release fentanyl product. Immediate-release fentanyl products 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. Appropriate specialist input should be sought.

Recommendations

- All strengths of each brand of immediate-release fentanyl product cost the same. Therefore, once the maintenance dose is reached (i.e. after titration) avoid prescribing doses as multiple dose units (unless this is essential to get the required dosage) as this increases the cost of treatment.
- If more than two to four episodes of breakthrough pain are experienced per day, the dose of the background long-acting opioid used for persistent pain should be re-evaluated.
- There are a number of different formulations of immediate-release fentanyl products available. They have different dosage instructions and pharmacokinetic profiles. To prevent potential for prescribing and dispensing errors:
  - » Products should be prescribed by brand to reduce this risk.
  - » Organisations may wish to restrict the number of products included on local formularies.

These recommendations do not apply to palliative care patients and when the recommendation is in line with NICE guidance and from a multidisciplinary team and/or other healthcare professional with a recognised specialism in palliative care.

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.[1] As the patent for fentanyl has expired, new patents can be applied to novel delivery systems and a variety of preparations are currently available. It is available as an immediate-release presentation in various dosage forms including buccal tablets, sublingual tablets, lozenges, films and nasal sprays.[2,3] The pharmacokinetic characteristics of these products vary, and they are not interchangeable.[1] Fentanyl is a schedule 2 Controlled Drug (CD) and therefore subject to the full CD requirements relating to prescriptions, safe custody, and the need to keep a CD register.[3]

All the immediate-release fentanyl products are only licensed for the treatment of breakthrough pain in adult patients receiving opioid therapy for chronic cancer pain (over 18 years old, except Actiq® and Cynril®, which are, licensed from 16 years old). Patients receiving maintenance opioid therapy are defined in the product literature as:[2,4-9]

- Those who are already receiving at least 60mg oral morphine daily or
- At least 25mg of transdermal fentanyl per hour or
- At least 30mg of oxycodone daily or
- At least 8mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

None of the available immediate release fentanyl products are licensed for any other type of pain, e.g. for pain during dressing changes or refractory migraine.[3]

Individual titration is required because the effective dose cannot be reliably predicted from the maintenance dose of opioid. Despite this, the use of doses proportional to the maintenance dose has been suggested (see table 1). Careful monitoring is required during initial or subsequent titration.[1]

Table 1. Immediate-release fentanyl products and selected prescribing information for adult doses[3-9]

Product	Presentation and strength	Dose titration	Maximum frequency of use	Maximum dose per episode
Abstral®	Sublingual tablets 100 micrograms 200 micrograms 300 micrograms 400 micrograms 600 micrograms 800 micrograms	Initially 100 micrograms repeated if necessary, after 15-30 minutes; adjust dose according to response - consult product literature.	Maximum 2 doses per pain episode. Doses to be given a minimum 2 hours apart.* If >4 pain episodes/24 hours, adjust background analgesia.#	800 micrograms
Actiq®	Lozenges 200 micrograms 400 micrograms 600 micrograms 800 micrograms 1200 micrograms 1600 micrograms	Initially 200 micrograms (over 15 minutes) repeated if necessary 30 minutes after first dose was commenced; adjust dose according to response - consult product literature. Once a successful dose has been established (i.e. on average, an episode is effectively treated with a single unit), patients should be maintained on this dose.	Maximum 2 doses per pain episode. Maximum of four Actiq® units per day. Minimum time interval not stated.* If >4 pain episodes/24 hours adjust background analgesia.#	At 1600 micrograms a second dose is only likely to be required by a minority of patients.
Cynril®	Lozenges 200 micrograms 400 micrograms 600 micrograms 800 micrograms 1200 micrograms 1600 micrograms	Initially 200 micrograms (over 15 minutes) repeated if necessary 30 minutes after first dose was commenced; adjust dose according to response - consult product literature. Once a successful dose has been established (i.e. on average, an episode is effectively treated with a single unit), patients should be maintained on this dose.	Maximum 2 doses per pain episode. Maximum of four Cynril® units per day. Minimum time interval not stated.* If >4 pain episodes/24 hours, adjust background analgesia.#	At 1600 micrograms a second dose is only likely to be required by a minority of patients.
Effentora®	Buccal tablets 100 micrograms 200 micrograms 400 micrograms 600 micrograms 800 micrograms	Initially 100 micrograms repeated if necessary after 30 minutes; adjust dose according to response - consult product literature.	Maximum 2 doses per pain episode. Doses to be given a minimum 4 hours apart.* Dose readjustment of the background opioid therapy may be required if patients consistently present with more than four pain episodes per 24 hours.#	800 micrograms
Instanyl®	Nasal spray 50 micrograms 100 micrograms 200 micrograms	Initially 50 micrograms into one nostril, repeated once if necessary, after 10 minutes; adjust dose according to response – consult product literature.	Maximum 2 sprays per pain episode. Doses to be given a minimum 4 hours apart.* If >4 pain episodes/24 hours, adjust background analgesia.#	400 micrograms

Product	Presentation and strength	Dose titration	Maximum frequency of use	Maximum dose per episode
PecFent®	Nasal spray 100 micrograms 400 micrograms	Initially 100 micrograms into one nostril; adjust dose according to response – consult product literature.	Maximum 2 sprays per pain episode. Doses to be given a minimum 4 hours apart.* If >4 pain episodes/24 hours, adjust background analgesia.#	800 micrograms

***The recommended interval between episodes stated in the table are in accordance with the BNF and the individual Summary of Product Characteristics (SPCs).[3-9] However, the Palliative Care Formulary recommends that in general, a minimum interval between treatments of ≥4hours is appropriate, on the basis that it was used by most studies, and more frequent dosing than four hourly appears to increase the maximum plasma concentration achieved with the subsequent dose of fentanyl.[1]**

#The BNF and the individual SPCs for immediate-release fentanyl products state that a maximum of four breakthrough pain episodes/24 hours can be treated; some state that if more than four breakthrough pain episodes are experienced in 24 hours, a review of the background analgesia is necessary.[3-9] However, the Palliative Care Formulary suggests that regular daily use of breakthrough medication twice daily or more should prompt a review and possible increase in the dose of the regular strong opioid.[1]

Immediate-release fentanyl products are included in NHS England and NHS Improvement's "Items which should not routinely be prescribed in primary care: Guidance for CCGs". These are items that are considered clinically effective, but where more cost-effective products are available, which includes products that have been subject to excessive price inflation.[2] There is also a National Institute for Health and Clinical Excellence (NICE) Do Not Do Recommendation which advises not to offer fast-acting fentanyl as first-line rescue medication for palliative care patients who can take oral opioids.[10]

All strengths and formulations of immediate-release fentanyl are category C in the Drug Tariff so the reimbursement price is based on various different brands.[11] In England and Wales £6.7 million is spent on the prescribing of fentanyl immediate-release products over the course of a year (NHSBSA September to November 2020). Reducing and optimising the use of immediate-release fentanyl products by using immediate-release morphine as the first-line choice (and immediate-release fentanyl only in limited circumstances where other short-acting opioids are unsuitable) has the potential to release significant savings. As with all switches, individual patient circumstances need to be borne in mind.

National guidance

The NICE clinical guideline palliative care for adults: strong opioids for pain relief [CG140], was published in May 2012. The guideline is aimed at patients with pain associated with advanced and progressive conditions including cancer, heart failure, chronic illness such as kidney, liver and respiratory disease, and neurodegenerative diseases. The guideline recommends the following for first-line treatment for breakthrough pain in patients who can take oral opioids:[12]

- Offer oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.
- Do not offer fast-acting fentanyl as first-line rescue medication (a NICE Do Not Do Recommendation).[10]
- If pain remains inadequately controlled despite optimising treatment, consider seeking specialist advice.

In November 2017 NHS England and NHS Clinical Commissioners published guidance on "Items which should not be routinely prescribed in primary care". The guidance was issued to support Clinical Commissioning Groups (CCGs) to ensure that they used their prescribing resources effectively and deliver best patient outcomes from the medicines that their local population used. Immediate-release fentanyl was included as it was categorised as 'items which are clinically effective, but where more cost-effective products are available, including products that have been subject to excessive price inflation.' The background and rationale for immediate-release fentanyl inclusion was due to the NICE Do Not Do Recommendation in NICE CG140[10,12] and because immediate-release fentanyl is only licensed for use in breakthrough chronic cancer pain in patients already using opioid therapy.[4-9] However, there are specific exceptions for people receiving palliative care reflecting NICE CG140 and the terms of the product licence. Immediate release fentanyl remained in version 2 of the guidance which was updated in July 2019.[2]

The guidance recommends:[2]

- Prescribers in primary care should not initiate immediate-release fentanyl for any new patient.
- CCGs should support prescribers in deprescribing immediate-release fentanyl in all patients and, where appropriate, ensure the availability of relevant services to facilitate this change.
- If, in exceptional circumstances, there is a clinical need for immediate-release fentanyl to be prescribed in primary care, this should be undertaken in a co-operation arrangement with a multi-disciplinary team and/or other healthcare professionals.

These recommendations do not apply to patients undergoing palliative care treatment and where the recommendation to use immediate-release fentanyl in line with NICE guidance [CG140], has been made by a multidisciplinary team and/or other healthcare professional with a recognised specialism in palliative care. The recommendations also do not apply to longer sustained release versions of fentanyl which come in patch form.[2]

The Palliative Care Formulary explains that breakthrough cancer pain generally has a relatively rapid onset (five to ten minutes) and short duration (45–60 minutes) but can range from under one minute to four to six hours. Oral morphine takes about 15–30 minutes to achieve meaningful pain relief and has a longer duration of effect (three to six hours). This helps to explain why many patients choose not to take a rescue dose of an oral opioid with every episode of breakthrough pain, particularly when predictable, mild in intensity, and of relatively short duration. Strategies to circumvent the mismatch between breakthrough pain duration and drug effect latency include:[1]

- Timing a predictable painful activity or procedure to coincide with the peak plasma concentration after a regular or rescue oral dose of morphine (one to two hours) or other strong opioid.
- Using routes of administration, e.g. buccal, intranasal, sublingual, which permit more rapid absorption of some (lipophilic) opioids, e.g. fentanyl.

Immediate-release fentanyl products cost substantially more than short-acting oral strong opioids and generally their use is reserved for when the latter are unsatisfactory. They are more effective than placebo, but direct comparison with oral morphine or each other is limited. The Palliative Care Formulary suggests the following in patients with cancer, taking regular strong opioids and experiencing breakthrough cancer pain:[1]

- Use immediate-release strong opioids first-line and titrate accordingly (include a trial of a solution if tablets are not adequate); only when inadequate with regards 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 the patient fulfils 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.

The Scottish Medicines Consortium (SMC) have advised that Abstral® sublingual tablets, Effentora® buccal tablets, Instanyl® nasal spray and PecFent® nasal spray, should be restricted for use within NHS Scotland for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain, when other short-acting opioids are unsuitable.[3,13-16] Abstral® offers an alternative to buccal administration at a reduced cost per administration.[13] Use of fentanyl nasal spray (Instanyl®) should be restricted to patients who are unsuitable for other short-acting oral opioids (e.g. oral morphine) as an alternative to other buccal and sublingual fentanyl preparations. It should be noted that the doses of fentanyl nasal spray are significantly lower than doses of fentanyl given by other routes of administration for this indication.[15] PecFent® nasal spray is restricted to use in patients unsuitable for short-acting oral opioids, as an alternative to other fentanyl preparations. Indirect comparison indicates broadly comparable efficacy to an oral transmucosal fentanyl formulation and an existing fentanyl nasal spray. Prescribers should be aware of the differing absorption and elimination characteristics of the available nasal fentanyl preparations.[16]

The All Wales Medicines Strategy Group (AWMSG) has also conducted appraisals of the fentanyl nasal sprays Instanyl® and PecFent®.[17,18]

Fentanyl intranasal spray (Instanyl®):[17]

- Instanyl® is recommended as an option for use within NHS Wales for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.
- Instanyl® should only be considered as an option for the management of breakthrough cancer pain when immediate-release oral opioids (e.g. morphine, oxycodone) are either inadequate or unsuitable.
- Instanyl® may be suitable for shared care but should be initiated by, and remain under the supervision of, a physician experienced in the management of opioid therapy in cancer patients.

Fentanyl intranasal spray (PecFent®):[18]

- PecFent® is recommended as an option for use within NHS Wales for the management of breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain.
- PecFent® should be initiated by, and remain under the supervision of, a specialist physician experienced in the management of opioid therapy in cancer patients.
- AWMSG is of the opinion that fentanyl (PecFent®) may be suitable for shared care within NHS Wales for the above indication.

The Northern Ireland Department of Health (NI DH) and the Health and Social Care Board (HSCB) have included immediate-release fentanyl on the 'Limited Evidence List'. Medicines on the Limited Evidence List should be reviewed to ensure that they are used only in the approved circumstances. For immediate-release fentanyl this is within the licensed indication and use in palliative care by a recognised multidisciplinary team professional is acceptable and appropriate patients should not have the medicine deprescribed.[19] Prescribers should NOT routinely use oral/nasal fentanyl products for non-cancer pain. Prescribing requires specialist knowledge and formulations are extremely expensive. If acute breakthrough analgesia is required, consideration should be given to the use of non-opioids or alternative opioids such as oral morphine.[20]

PrescQIPP resources

PrescQIPP have a number of resources which are relevant to this bulletin and are hyperlinked below.

Bulletin 256: Dependence forming medications - This bulletin provides an overview of potentially dependence forming medicines (DFMs) including high dose opioids, hypnotics, benzodiazepines, gabapentin and pregabalin and signposts to PrescQIPP resources which support medicines optimisation projects in this area. Implementation tools include prescribing information for fentanyl lozenges.

Low Priority Prescribing Webkit - This contains resources that have been developed to support the implementation of the NHS England low priority prescribing guidance. This includes:

- Bulletin 203: Items which should not routinely be prescribed in primary care - an overarching document that supports the implementation of the NHS England 'Items which should not routinely be prescribed in primary care' guidance and includes information in immediate-release fentanyl.
- Patient Information Leaflets - these leaflets explain why certain medicines are included in the NHS England guidance and where patients can find further help. Leaflets include "Changes to immediate-release fentanyl prescribing".
- Data – This dashboard incorporates monitoring for all three phases of the NHS England low priority prescribing guidance. Data on immediate-release fentanyl is included in phase 1.

- LPP Masterclass - Fentanyl IR - Linda Lord, Chief Pharmacist for NHS West Suffolk Clinical Commissioning Group presented a webinar covering strategies used in West Suffolk for reducing inappropriate prescribing of immediate-release fentanyl.
- The Pain Webkit - brings together all the PrescQIPP pain resources. This includes resources on controlled drugs, opioid prescribing in chronic pain, and shared good practice examples.

Bulletin 252: Medicines without harm - These resources support the implementation of local campaigns for the World Health Organisation (WHO) global patient safety challenge, medication without harm. There is an overarching bulletin and four different campaigns: insulins, NSAIDs, sodium valproate and dependence forming medicines including opioids (e.g. immediate-release fentanyl), benzodiazepines, Z-drugs, gabapentin and pregabalin.

Clinical effectiveness

Evidence for breakthrough pain in chronic cancer pain

The rationale for including immediate-release fentanyl in NHS England and NHS Clinical Commissioners "Items which should not routinely be prescribed in primary care" was that NICE CG140 on palliative care for adults: strong opioids for pain relief states - Do not offer fast-acting fentanyl as first-line rescue medication. Due to this recommendation from NICE and that immediate-release fentanyl is only licensed for use in cancer, the joint clinical working group considered that it was suitable for inclusion in the guidance with specific exceptions for people receiving palliative care reflecting NICE and the terms of the product licence.[2,12]

The NICE CG140 guideline development group (GDG) considered data from one randomised controlled trial and two systematic reviews (including a Cochrane review) that compared immediate-release morphine with immediate-release fentanyl. The GDG was satisfied that there was limited evidence to suggest that fentanyl is more clinically effective than immediate-release morphine (and immediate-release oxycodone) for the management of breakthrough pain. However, it felt the cost impact of recommending fentanyl over immediate-release morphine or oxycodone would be considerable and therefore could not be justified. The GDG agreed to recommend that immediate-release fentanyl is not offered as first-line rescue medication.[21]

In May 2014 NICE published an evidence update on opioids in palliative care (Evidence Update 58) which identified a 2013 Cochrane review assessing opioid analgesics for managing breakthrough pain in patients with cancer.[22,23] This was an update of the Cochrane review considered by the GDG and included 15 studies, however only two were considered to be of direct relevance to NICE CG140. One study compared oral fentanyl versus oral morphine, and the other study nasal fentanyl versus oral morphine. Data from both of these trials was examined for the original guideline. From a meta-analysis of the two studies, transmucosal fentanyl was more effective than oral morphine for pain intensity difference at 15 minutes (mean difference=0.37, 95% CI 0.00 to 0.73, p=0.048; two studies, n=154). Other meta-analyses showed that transmucosal fentanyl was more effective than placebo at 10, 15 and 30 minutes ($p<0.00001$ for all three time points). The authors concluded that oral and nasal transmucosal fentanyl seem to be effective treatments for breakthrough cancer pain and appear to be more effective than oral morphine for pain intensity at 15 minutes. However, the benefits of transmucosal fentanyl over oral morphine remain unlikely to outweigh its substantial additional cost. The average cost of treating a breakthrough event with fentanyl was calculated to be approximately 50 times more than with morphine in the full version of NICE CG140. This evidence is therefore unlikely to have an impact on the statement in NICE CG140: do not offer fast-acting fentanyl as first-line rescue medication.[23]

Feedback on the 2013 version of the Cochrane review stated that the review was misleading and questioned the statistical and clinical significance of the findings. As the original authors were unavailable to update the review, the Cochrane Editorial Unit withdrew it. The feedback did not agree with the authors' results that when compared with placebo or oral morphine, participants gave lower pain intensity and higher pain relief scores for transmucosal fentanyl formulations at all time points. They commented that the outcome at 15 minutes (the most important to obtain a quick relief of pain), for transmucosal opioid versus oral morphine and for oral transmucosal fentanyl citrate versus intravenous morphine, failed to show statistically significant differences with oral morphine (mean difference 0.37, CI 95% 0.00-0.73) and with intravenous morphine (mean difference 0.80, CI 95% 0.00-1.60) so the results had no clinical relevance. The feedback also stated that the review did not provide any data for longer time intervals such as 30, 45 or 60 minutes so did not reflect all time points. The feedback concluded that the review did not show that the use of oral and nasal transmucosal fentanyl is an effective alternative to morphine for patients with breakthrough cancer pain.[24]

Two randomised controlled trials from 2014 comparing immediate-release fentanyl to an active comparator for breakthrough cancer pain have been identified. One compared two different formulations of fentanyl nasal spray. The small, unblinded study (n=70) found both delivery systems, in doses proportional to the basal opioid regimen, provided significant analgesia within 10 minutes, without producing relevant adverse effects. Most of patients did not find substantial preferences.[25] The other compared sublingual fentanyl to oral morphine solution.[26] Although the company funded study reported a statistically significant difference between treatments favouring sublingual fentanyl, the study size (n=40) and methodological limitations (including lack of proper randomisation) mean that further studies addressing this question are needed.

In 2017 an overview of Cochrane reviews assessed the analgesic efficacy of opioids in cancer pain and reported on adverse events associated with their use. The reviews included fentanyl but by transdermal administration rather than transmucosal fentanyl. The review found that the amount and quality of evidence around the use of opioids for treating cancer pain is disappointingly low, although the studies indicate that around 19 out of 20 people with moderate or severe pain who are given opioids and can tolerate them, should have that pain reduced to mild or no pain within 14 days. Most people will experience adverse events with opioids. Between one in ten and two in ten people treated with opioids will find these adverse events intolerable, leading to a change in treatment.[27] Another Cochrane study reviewed the use of opioids, including fentanyl, for cancer related pain in children and adolescents. It was unable to identify any studies eligible for inclusion as none included participants aged from birth to seventeen years. The authors concluded that there is no evidence from randomised controlled trials to support or refute the use of opioids to treat chronic cancer related pain and they were unable to

comment on the efficacy or harm from the use of opioids to treat chronic cancer related pain in children and adolescents.[28]

Evidence in non-cancer pain

A review of fentanyl use in neuropathic pain in adults considered trials which included any dose, and by any route of administration. Only one study met the inclusion criteria in which participants received one-day skin patches for one month, the rescue medication was morphine not immediate-release fentanyl. The authors concluded that there was insufficient evidence to support or refute the suggestion that fentanyl works in any neuropathic pain condition.[29]

A Cochrane review assessed the analgesic efficacy and adverse events of opioids used to treat chronic non-cancer pain in children and adolescents aged between birth and seventeen years, in any care setting. No studies were eligible for inclusion in the review, therefore the authors concluded that there is no evidence to support or refute the use of opioids for treating chronic non-cancer pain in children and adolescents.[30]

A 2014 Cochrane review looked at intranasal fentanyl for the management of acute pain in children. Three studies (313 participants) were included, one compared intranasal fentanyl versus intramuscular morphine; another compared intranasal fentanyl versus intravenous morphine. The third study compared standard concentration intranasal fentanyl versus high concentration intranasal fentanyl. All three studies reported a reduction in pain score following intranasal fentanyl administration. The review concluded that intranasal fentanyl may be an effective analgesic for the treatment of patients with acute moderate to severe pain, and its administration appears to cause minimal distress to children. However, this review does not allow any definitive conclusions regarding whether intranasal fentanyl is superior, non-inferior or equivalent to intramuscular or intravenous morphine. The review had limitations, which included that there were few eligible studies for inclusion (three); no study examined the use of intranasal fentanyl in children younger than three years of age; no study included children with pain from a "medical" cause (e.g. abdominal pain seen in appendicitis); and all eligible studies were conducted in Australia.[31]

Safety

In response to a number of deaths and patient safety incidents associated with opioid dosing errors, the National Patient Safety Agency (NPSA) produced a Rapid Response Report on opioid medicines in 2008, which included fentanyl. The aim of the guidance was to ensure that all healthcare professionals involved in the prescribing, dispensing or administration of opioids were aware that they have the responsibility to check that an intended opioid dose is safe and appropriate for that patient. They must also be familiar with the characteristics (e.g. dosing increments and side effects) of the opioid being used.[32]

In 2007, after reports of serious overdoses and deaths in the USA, the Food and Drug Administration (FDA) issued a safety warning about the use of Fentora® (Effentora® in the UK). Factors which contributed to the adverse drug events included improper:[1]

- 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. like-for-like swap from Actiq® to Effentora®.

Thus, these products need to be used correctly, specifically:[1]

- Do not use in opioid naïve (non-tolerant) patients, including those who only take strong opioids as needed.
- They are contraindicated in the management of acute or postoperative pain, including 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.

In 2010, the FDA determined that a Risk Evaluation and Mitigation Strategy (REMS) would be necessary to ensure the benefits of transmucosal immediate-release fentanyl products outweigh their risks. The REMS was approved in December 2011 and was intended to make sure that transmucosal immediate-release fentanyl products are prescribed only to appropriate patients. The REMS also includes measures that are designed to limit use only in opioid-tolerant patients; to avoid inappropriate conversion between transmucosal immediate-release fentanyl medicines; to reduce accidental exposure; and to educate prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.[33]

In 2019 an assessment of the FDA REMS evaluated the knowledge assessments of pharmacists, prescribers, and patients regarding appropriate use of transmucosal immediate-release fentanyl products. Surveys of 796 individuals 12 months after the REMS program inception indicated that 92.1% of pharmacists, 88.4% of prescribers, and 97.4% of patients correctly reported that transmucosal immediate-release fentanyl products are contraindicated in opioid-nontolerant patients. However, a claims-based analyses 60 months after the REMS program inception indicated that 34.6% to 55.4% of patients prescribed transmucosal immediate-release fentanyl products were opioid-nontolerant.[34]

Prescribing considerations

Contraindications

All opioids are contraindicated in acute respiratory depression; comatose patients; head injury; raised intracranial pressure and if there is a risk of paralytic ileus.[3] Contraindications for all immediate-release fentanyl formulations are:[4-9]

- Hypersensitivity to the active substance or to any of the excipients.
- Patients without maintenance opioid therapy (increased risk of respiratory depression).
- Severe respiratory depression or severe obstructive lung conditions.
- Treatment of acute pain other than breakthrough pain.

In addition to the above Actiq® and Cynril® are also contraindicated when:[5,6]

- Simultaneous use of monoamine oxidase inhibitors (MAO inhibitors), or within 2 weeks after the cessation of the use of MAO inhibitors.

In addition to the contraindications for all immediate-release fentanyl formulations, Instanyl® is also contraindicated in:[8]

- Patients being treated with medicinal products containing sodium oxybate.
- Previous facial radiotherapy.
- Recurrent episodes of epistaxis.

Cautions and special warnings for prescribing

Cautions for all opioids include:[3]

- Adrenocortical insufficiency (reduced dose is recommended)
- Asthma (avoid during an acute attack)
- Central sleep apnoea (dose-dependent increased risk, consider total opioid dose reduction)
- Convulsive disorders
- Current or history of mental health disorder (prolonged use may lead to drug dependence and addiction, even at therapeutic doses)

- Current or history of substance use disorder (prolonged use may lead to drug dependence and addiction, even at therapeutic doses)
- Debilitated patients (reduced dose is recommended in adults)
- Diseases of the biliary tract
- Elderly (reduced dose is recommended)
- Hypotension
- Hypothyroidism (reduced dose is recommended)
- Impaired respiratory function (avoid in chronic obstructive pulmonary disease)
- Inflammatory bowel disorders
- Myasthenia gravis
- Obstructive bowel disorders
- Prostatic hypertrophy (in adults)
- Shock
- Urethral stenosis (in adults)

However, for the control of pain in terminal illness, the cautions listed should not necessarily be a deterrent to the use of opioid analgesics.[3]

Fentanyl should also be used with caution in:[3-9]

- Cerebral tumour
- Diabetes mellitus (Actiq® and Cynril® lozenges contain sugar)
- Impaired consciousness
- Patients with previous or pre-existing bradyarrhythmias
- Hypovolaemia
- Mucositis - with buccal use absorption from oral preparations may be increased, caution during dose titration (in adults)

Patients and their carers must be instructed that an immediate-release fentanyl preparation contains an active substance in an amount that can be fatal to a child, and therefore to keep the preparation out of the reach and sight of children.[4-9]

As with other opioids, in case of insufficient pain control in response to an increased dose of fentanyl, the possibility of opioid-induced hyperalgesia should be considered. A fentanyl dose reduction or discontinuation of fentanyl treatment or treatment review may be indicated.[4-9]

Before immediate-release fentanyl therapy is initiated, it is important that the patient's long-acting opioid treatment used to control their persistent pain has been stabilised.[4-9]

Renal and hepatic impairment

Immediate-release fentanyl should be administered with caution to patients with liver or kidney dysfunction, especially during the titration phase. The use of immediate-release fentanyl in patients with hepatic or renal impairment may increase the bioavailability of fentanyl and decrease its systemic clearance, which could lead to accumulation and increased and prolonged opioid effects.[4-9] The BNF advises to avoid use or reduce dose in renal impairment as increased cerebral sensitivity occurs.[3]

Older, cachectic or debilitated patients may have a lower fentanyl clearance, which could cause a longer terminal half-life.[4,8]

Pregnancy and breastfeeding

The safety of fentanyl in pregnancy has not been established. Studies in animals have shown reproductive toxicity, with impaired fertility in rats. The potential risk for humans is unknown. Fentanyl should only be used during pregnancy when clearly necessary. Long-term treatment during pregnancy may cause withdrawal symptoms in the new-born infant.[4-9]

Fentanyl should not be used during labour and delivery (including caesarean section) since fentanyl crosses the placenta and may cause respiratory depression in the foetus or in the new-born infant.[4-9] Also, gastric stasis and inhalation pneumonia has been reported in the mother if opioid analgesics are used during labour.[3]

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breastfed child. Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 5 days after the last administration of fentanyl.[4-9]

Dependence, abuse and addiction

Repeated administration of opioid analgesics such as fentanyl, is associated with the development of tolerance, physical and/or psychological dependence. Iatrogenic addiction following therapeutic use of opioids is known to occur.[4-9] The risk is considered low in cancer patients with breakthrough pain but may be higher in those patients with a history of substance abuse and alcohol dependence. All patients treated with opioids require careful monitoring for signs of abuse and addiction.[5,6]

Adverse effects

For all opioids common or very common side-effects include arrhythmias; confusion; constipation; dizziness; drowsiness; dry mouth; euphoric mood; flushing; hallucination; headache; hyperhidrosis; hypotension (with high doses); miosis; nausea (more common on initiation); palpitations; respiratory depression (with high doses); skin reactions; urinary retention; vertigo; visual impairment; vomiting (more common on initiation); withdrawal syndrome. Drug dependence and dysphoria are uncommon.[3]

Respiratory depression is a major concern with opioid analgesics, and it may be treated by artificial ventilation or be reversed by naloxone.[3]

Topical effects for immediate-release fentanyl are less common and formulation-dependent, but include oral and nasal discomfort, inflammation or ulceration, rhinorrhoea, epistaxis, sore throat, dysgeusia.[1] Product specific adverse effects are:

- Abstral® - The most frequently observed adverse reactions include nausea, constipation, somnolence and headache.[4]
- Actiq® and Cynril® - Application site reactions including gum bleeding, irritation, pain, mouth ulcer (common) and dental caries (uncommon).[1,5,6]
- Effentora® - Application site reactions including bleeding, pain, mouth ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles are very common. Hypersensitivity reactions including rash, erythema, lip and face swelling, and urticaria are reported rarely.[7]
- Instanyl® - common adverse reactions include vertigo, flushing, throat irritation and hyperhidrosis.[8]
- PecFent® - disorientation and pruritus are common adverse reactions.[9]

Cases of adrenal insufficiency have been reported with opioid use including fentanyl lozenges, more often following greater than one month of use. Wean the patient off the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers.[5,6]

Interactions

Fentanyl is metabolised by CYP3A4 isoenzyme in the liver and intestinal mucosa. Substances that inhibit CYP3A4 activity such as grapefruit juice, macrolide antibiotics (e.g. erythromycin), azole antifungal agents (e.g. ketoconazole, itraconazole and fluconazole) or certain protease inhibitors (e.g. ritonavir) may

increase the bioavailability of fentanyl by decreasing its systemic clearance, potentially enhancing or prolonging opioid effects. Caution is advised if fentanyl is given concomitantly with CYP3A4 inhibitors.[4-9] Patients receiving IR fentanyl concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done with caution.[7-9]

Co-administration with agents that induce CYP3A4 activity such as antimycobacterials (e.g. rifampin, rifabutin), anticonvulsants (e.g. carbamazepine, phenytoin, and phenobarbital) herbal products (e.g. St John's wort, Hypericum perforatum) may reduce the efficacy of fentanyl.[4-9] CYP3A4 inducers exert their effect in a time-dependent manner and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least two weeks to decline. Patients receiving fentanyl who stop therapy with, or decrease the dose of CYP3A4 inducers, may be at risk of increased fentanyl activity or toxicity. Fentanyl should be used with caution if administered concomitantly with CYP3A4 inhibitors and/or inducers.[4]

Concomitant use of other CNS depressants, such as other morphine derivatives (analgesics and antitussives), general anaesthetics, skeletal muscle relaxants, sedative antidepressants, sedative H1 antihistamines, barbiturates, anxiolytics (i.e. benzodiazepines), hypnotics, antipsychotics, phenothiazines, tranquillisers, alcohol, clonidine and related substances may produce increased CNS depressant effects which may result in a fatal outcome.[4-9] Therefore, the use of any of these medicinal products concomitantly with IR fentanyl requires special patient care and observation.[8] The lowest effective dosages and minimum durations of concomitant use should be chosen. Patients should be closely monitored for signs and symptoms of respiratory depression and sedation.[7]

In March 2020 the Medicines and Healthcare products Regulatory Agency (MHRA) reminded healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death. Healthcare professionals are advised to only co-prescribe if there is no alternative and, if necessary, the lowest possible doses should be given for the shortest duration. Patients should be closely monitored for signs of respiratory depression at initiation of treatment and when there is any change in prescribing, such as dose adjustments or new interactions. Patients should be informed of the signs and symptoms of respiratory depression and sedation, and advised to seek urgent medical attention should these occur.[35]

Co-administration of fentanyl with a serotoninergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.[4-9] Abstral®, Effentora®, Instanyl® and PecFent® are not recommended for use in patients who have received MAOIs within 14 days because severe and unpredictable potentiation by MAOIs has been reported with opioid analgesics.[4,7-9] Simultaneous use of Actiq® and Cynril® with monoamine oxidase inhibitors (MAOIs), or within two weeks after cessation of the use of MAOIs inhibitors is contraindicated.[5,6]

The concomitant use of partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients.[4-9]

Concomitant use of nasally administered oxymetazoline has been shown to decrease the absorption of Instanyl® and PecFent®. The concomitant use of nasally administered vasoconstrictive decongestants during titration is therefore not recommended as this may lead to patients titrating to a dose that is higher than required.[8,9] IR fentanyl treatment may also be less effective in patients with rhinitis when administered concomitantly with a nasal vasoconstrictive decongestant. If this occurs, patients should be advised to discontinue their decongestant.[9]

Concomitant use of Instanyl® and PecFent® and other medicinal products (other than oxymetazoline)

administered via the nose has not been evaluated in the clinical trials. It is recommended that alternative administration forms should be considered for concomitant treatment of concurrent diseases that can be treated via nasal administration[8] or if this is not possible, avoid other intranasal administration within 15 minutes of dosing with IR fentanyl.[9]

Overdose

The symptoms of fentanyl overdose include altered mental status, loss of consciousness, coma, cardiorespiratory arrest, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.[4-9]

Immediate management of opioid overdose includes removal of any remaining fentanyl preparations from the mouth (if applicable), ensuring a patent airway, physical and verbal stimulation of the patient and an assessment of the level of consciousness, ventilatory and circulatory status, and assisted ventilation (ventilatory support) if necessary.[4-9] The specific antidote naloxone hydrochloride is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma.[3]

Treatment cessation

Immediate-release fentanyl preparations should be discontinued immediately if the patient no longer experiences breakthrough pain episodes. There should be no noticeable effects on cessation of treatment, but possible symptoms of withdrawal are anxiety, tremor, sweating, paleness, nausea and vomiting.[4-9]

If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor in order to manage a gradual downward opioid titration in order to avoid the risk of abrupt withdrawal effects.[4-9]

The availability of a number of different formulations of immediate-release fentanyl products with similar strengths but different dosage instructions and pharmacokinetic profiles creates potential for prescribing and dispensing errors. Products should be prescribed by brand to reduce this risk and organisations may wish to restrict the number of products included on local formularies.

There have been a number of adverse incidents reported involving fentanyl immediate-release preparations. In particular, the lozenge preparation resembles 'lollipops' and should not be left unattended.[20] Safe storage and disposal of products is essential. They must be kept out of reach of children; accidental deaths have occurred.[1]

Patient factors

The patient's circumstances need careful consideration to ensure they fulfil the necessary requirements for use of a transmucosal product. This will include their current opioid dose and their ability to access, use, store and dispose of the product reliably. When the decision to use an immediate-release fentanyl product has been made, consideration should be given to which type of transdermal fentanyl product may be more suitable for an individual and patients may have an individual preference.[1]

Nasal products:[1]

- Generally, Generally, work quicker and the pain relief is shorter (less oral absorption) than the sublingual/buccal route.
- They may be preferred in the presence of severe dry mouth or mucositis.
- PecFent® works slightly more slowly than Instanyl® but has a safer accountable delivery system and is cheaper.

Sublingual/buccal:[1]

- May be preferred if the patient has nose bleeds.
- There is little difference between the sublingual/buccal preparations in terms of efficacy.
- Abstral® dissolves the quickest, making it the most convenient to use.

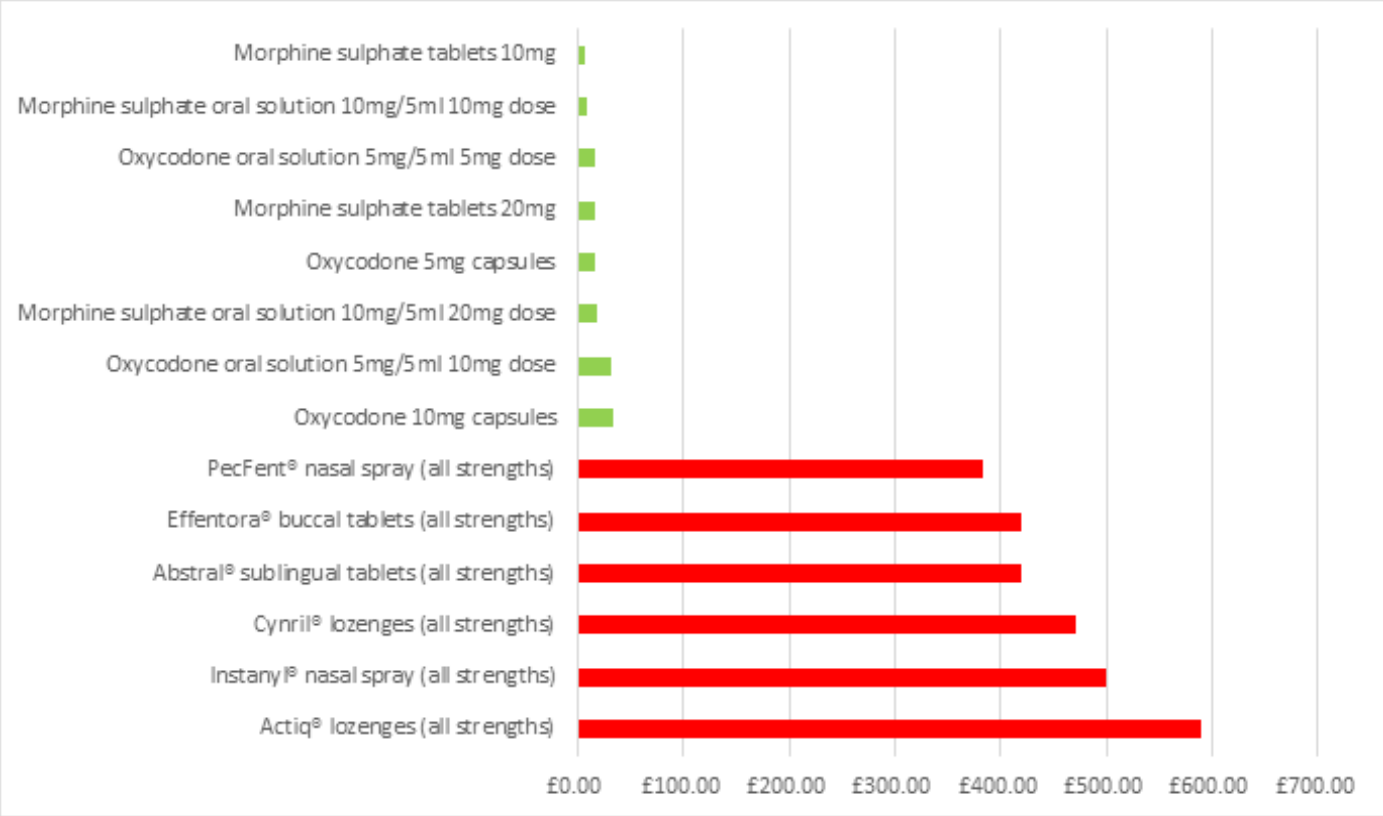
Costs

There is a significant difference in cost between immediate-release fentanyl products and other immediate-release strong opioids such as morphine and oxycodone. Table 2 and chart 1 illustrate the cost differences. Example morphine and oxycodone doses are included for comparison; the list is not exhaustive for the strengths available or the dosages used in practice and is for illustrative purposes only.

Table 2. Immediate-release fentanyl, morphine and oxycodone products and price comparison.[3,11]

Product	Product cost per dose unit	Cost of 28 days treatment with three doses/day
Abstral® sublingual tablets (all strengths)	£4.99	£419.16
Actiq® lozenges (all strengths)	£7.02	£589.40
Cynril® lozenges (all strengths)	£5.60	£470.40
Effentora® buccal tablets (all strengths)	£4.99	£419.16
Instanyl® nasal spray (all strengths)	£5.95	£499.80
PecFent® nasal spray (all strengths)	£4.56	£383.04
Morphine sulphate tablets 10mg	£0.09	£7.96
Morphine sulphate tablets 20mg	£0.19	£15.91
Morphine sulphate oral solution 10mg/5ml 10mg dose	£0.11	£9.07
Morphine sulphate oral solution 10mg/5ml 20mg dose	£0.22	£18.14
Oxycodone 5mg capsules	£0.20	£17.15
Oxycodone 10mg capsules	£0.41	£34.29
Oxycodone oral solution 5mg/5ml 5mg dose	£0.19	£16.31
Oxycodone oral solution 5mg/5ml 10mg dose	£0.39	£32.63

Chart 1. Immediate-release fentanyl, morphine and oxycodone products and price comparison.[3,11]



Prescribing review and switching options

Local policy should outline the circumstances in which immediate-release fentanyl can be considered, which products can be prescribed and who can prescribe them. Any review of prescribing should reflect local as well as national guidelines.

- Prescribers in primary care should not initiate immediate-release fentanyl for any new patient.[2]
- Offer oral immediate-release morphine for the first-line rescue medication of breakthrough pain in patients on maintenance oral morphine treatment.[12]
- Support prescribers in deprescribing or switching immediate-release fentanyl in all patients and, where appropriate. Ensure the availability of relevant services to facilitate this change.[2]
  - » Immediate-release fentanyl preparations should be discontinued immediately if the patient no longer experiences breakthrough pain episodes.[4-9]
  - » Patients receiving immediate-release fentanyl who are still experiencing breakthrough pain and have not had immediate-release morphine first-line should be considered for a switch. The SPCs for immediate-release fentanyl preparations do not offer guidance on switching to alternative opioids such as morphine[4-9] The standard dose of a strong opioid for breakthrough pain is usually one-tenth to one-sixth of the regular 24-hour dose, repeated every two to four hours as required (up to hourly may be needed if pain is severe or in the last days of life).[3]
- If, in exceptional circumstances, there is a clinical need for immediate-release fentanyl to be prescribed in primary care, this should be undertaken in a co-operation arrangement with a multi-disciplinary team and/or other healthcare professional and be clearly documented in the patient's record.[2]
  - » Patients receiving the most costly immediate-release fentanyl products (Actiq® lozenges, Instanyl® nasal spray) who can't be switched to immediate-release morphine could be considered for a switch to a less costly immediate-release fentanyl product (see table 2 for prices and chart 1 for cost comparison).

  - Immediate-release fentanyl products 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.[1]
  - Appropriate specialist input should be sought.
  - Table 3 below provides a guide to the bioavailability of the various products, together with an estimated time to onset of action.
- On switching, review and optimise the person's laxative and anti-emetic treatment to ensure side-effects are being effectively managed.[12]
- If more than two to four episodes of breakthrough pain are experienced per day, then the dose of the long-acting opioid used for persistent pain should be re-evaluated.[3-9]
- All strengths of each brand of immediate-release fentanyl product cost the same.[11] Once the maintenance dose is reached (i.e. after titration) avoid prescribing doses as multiple dose units (unless this is essential to get the required dosage) as this increases the cost of treatment.
- Immediate-release fentanyl should be prescribed by brand for safety reasons; any generic prescribing should be reviewed.
- Immediate-release fentanyl products are licensed only for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain.[3-9] Use outside of the licence (e.g. for non-cancer pain or for patients not taking at least 60 mg of oral morphine daily or equivalent) has safety implications and should be reviewed. Where such use is deemed to be appropriate, consider if it would be more appropriate for the relevant specialist to prescribe and manage it.[1]

Table 3. Bioavailability of the immediate-release fentanyl products and estimated time to onset of action.[36]

	Bioavailability	Time to response (minutes)
Actiq® lozenges	50%	20-40
Effentora® buccal tablets	65%	20
Abstral® sublingual tablets	54%	22.5
Instanyl® nasal spray	89%	12-15
PecFent® nasal spray	Not available	15-20

In most cases, when switching between different opioids, the calculated dose-equivalent must be reduced to ensure safety. The starting point for dose reduction from the calculated equi-analgesic dose is around 25-50%. Some key messages relating to dose equivalents and changing opioids:[37]

- Switching from one opioid to another should only be recommended or supervised by a healthcare practitioner with adequate competence and sufficient experience. If uncertain, ask for advice from a more experienced practitioner.
- Opioid rotation or switching may be considered if a patient obtains pain relief with one opioid and is suffering severe adverse effects.
- When converting from one opioid to another, the initial dose depends on the relative potency of the two drugs and route of administration.
- An individualised approach is necessary.
- Conversion factors are an approximate guide only because comprehensive data are lacking and there is significant inter-individual variation.
- In most cases, when switching between different opioids, the calculated dose-equivalent must be reduced to ensure safety. The starting point for dose reduction from the calculated equi-analgesic dose is around 25-50%.

- A dose reduction of at least 50% is recommended when switching at high doses (e.g. oral morphine or equivalent doses of 500mg/24 hours or more), in elderly or frail patients, or because of intolerable undesirable effects.
- The half-life and time to onset of action of the two drugs needs to be considered when converting so that the patient does not experience breakthrough pain or receive too much opioid during the conversion period.
- Once the conversion has occurred, the dose of new opioid should be titrated carefully according to individual response and the patient monitored closely for side effects and efficacy, especially when switching at high doses.
- Withdrawal symptoms (e.g. sweating, yawning and abdominal cramps, restlessness, anxiety) occur if an opioid is stopped/dose reduced abruptly.

Savings

In England and Wales £6.7 million is spent on the prescribing of immediate-release fentanyl products over the course of a year (NHSBSA September to November 2020). The table below illustrates the significant savings that could be made by reducing and optimising the use of immediate-release fentanyl products.

Table 4. Illustration of savings from switching or optimising immediate-release fentanyl products.

	England and Wales	Per 100,000 patients
Annual savings if 10th percentile of cost per 1000 patients reached by all currently above it	£3,847,243	£6,017
Annual savings if 25th percentile of cost per 1000 patients reached by all currently above it	£2,878,427	£4,502
Annual saving if all use of Actiq® was switched to an alternative immediate-release fentanyl product (with a cost of £4.99 or less per dose)	£242,522	£379

Summary

- Immediate-release fentanyl is available in various dosage forms.[3-9] The pharmacokinetic characteristics of these products vary, and they are not interchangeable.[1] All formulations are only licensed for breakthrough pain in adults receiving opioid therapy for chronic cancer pain.[4-9]
- Immediate-release fentanyl products should not be routinely be prescribed in primary care as they are considered clinically effective, but more cost-effective products are available.[2] NICE (CG140) advises offering oral immediate-release morphine for the first-line rescue medication for breakthrough pain, not fast-acting fentanyl (NICE Do Not Do Recommendation).[10,12]
- There is limited evidence that immediate-release fentanyl gives better pain relief at 15 minutes than immediate-release morphine, however the clinical significance and the quality of the available data has been questioned. For a minority of patients for whom morphine or other strong opioids are unsuitable they offer an alternative option, this should be documented in the patient record.
- Careful patient selection by appropriately skilled clinicians is essential to ensure both safe and cost-effective use of these medicines. A patient's circumstances should be considered carefully to ensure the patient fulfils 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.[1]

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-285-fentanyl/
Implementation tools	
Data pack	https://data.prescqipp.info/views/B285_Fentanyl/FrontPage?:iid=1&:isGuestRedirectFromVizportal=y&:embed=y

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