

# London New Drugs Group APC/DTC Briefing Document

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# Fentanyl preparations for breakthrough cancer pain

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#### Summary

### The drug and the review

- Immediate-release (IR) fentanyl is used to treat breakthrough pain, a transient exacerbation of otherwise controlled chronic background pain.
- The aim of this review is to evaluate the currently available IR fentanyl preparations (Abstral sublingual tablets, Actiq lozenges and Effentora buccal tablets) plus the newly licensed intranasal formulation (Instanyl), and to discuss whether the products are interchangeable and when it is most appropriate to use each one. The review will not discuss the analgesic efficacy of fentanyl per se, as this is well established, or the use of strong opioids in palliative care, but will evaluate studies that compare the different fentanyl IR products.
- Reviews on the use of strong opioids in palliative care, including the use of fentanyl lozenges, can be found at: <u>http://www.npc.co.uk/ebt/merec/ pain/otherback/resources/merec\_briefing\_no22.pdf</u> and at <u>http://</u> www.nyrdtc.nhs.uk/docs/dud/DU\_63\_OPIOID.pdf.
- A review on fentanyl buccal tablets can be found at: <u>http://</u> <u>www.nelm.nhs.uk/en/NeLM-Area/Evidence/Drug-Specific-Reviews/</u> <u>Fentanyl-buccal-tablets/</u>.

# Background

- Breakthrough cancer pain is a transitory exacerbation of pain that occurs in patients who have otherwise well controlled persistent pain. It is though to occur in 50-90% of patients with cancer pain.
- There is no NICE guidance on the treatment of breakthrough cancer pain.
- The Scottish Medicines Consortium have approved both fentanyl buccal tablets (Effentora) and fentanyl sublingual tablets (Abstral) are for restricted use for treating breakthrough pain in adults who are already receiving maintenance opioid therapy for chronic cancer pain. Abstral® use is restricted to patients who are unsuitable for any other short-acting opioid, such as oral morphine.

#### Literature search

- The following databases were searched for information relating to fentanyl or fentanyl citrate, given by buccal, intranasal or sublingual administration, for cancer pain. Embase, Medline, IDIS (see end of document for search terms used).
- Cephalon (UK) Ltd, ProStraken and Nycomed UK Ltd were contacted.

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- No studies comparing the fentanyl products with each other were identified. The majority of trials were placebo controlled.
- One mixed treatment comparison study compared the evidence from placebo-controlled trials of three formulations of fentanyl: fentanyl buccal tablets, orotransmucosal fentanyl citrate and in-tranasal fentanyl spray, and a trial comparing orotransmucocal fentanyl in patients already using immediate release morphine sulphate. This has been published as a conference poster.
- All three fentanyl products were more effective than placebo in treating breakthrough cancer pain. Pain relief was attained within 10-15 minutes (the earliest time points that pain was assessed). Pain relief obtained with the morphine sulphate tablets was similar to that with placebo. The trials vary in design, hence the differences in assessment times.
- Intranasal fentanyl provided a greater reduction in pain intensity than the buccal and orotransmucosal products at each time point assessed (10, 20 and 30 minutes for the intranasal formulation and 15, 30 and 45 minutes for the buccal and orotransmucosal formulations).
- Orotransmucosal fentanyl produced significantly lower pain intensity scores than morphine sulphate at all time points, as well as greater pain relief.
- All immediate release fentanyl products give pain relief within 10-15 minutes of administration. Maximum plasma concentrations are reached faster with fentanyl nasal spray than with the oral/ buccal formulations.

## **Critical evaluation**

- There is a lack of evidence directly comparing fentanyl products for breakthrough cancer pain.
- The mixed treatment comparison is limited by the fact that randomisation and study design can differ across the trials. Patient characteristics were similar so bias may not be a problem.
- In the trial comparing fentanyl with morphine, the morphine dose was not obtained in the same protocol-driven way in which the fentanyl dose was identified, and there was a time-lag between setting the morphine dose and identifying the fentanyl dose. If the patients were not satisfied with pain controlled achieved with morphine, the results may have been biased towards the fentanyl product. Morphine sulphate solution is absorbed faster than tablets, and would have been a more suitable comparator product to the orotransmucosal products.

#### Potential benefits over existing technologies

• The wide range of products makes it easier to individualise treatment for each patient (but see disadvantages below). For example, intranasal fentanyl may be easier to administer to patients with a dry mouth, than an oral product. It should be noted that oral morphine solution is another suitable alternative product for patients with a dry mouth who are still able to swallow.

#### Potential disadvantages over existing technologies

- The wide range of fentanyl products can lead to errors in dosing due to differences in pharmacokinetic/dynamic profiles. The products are not interchangeable.
- Switching from one product to another must not be done at a 1:1 ratio due to differences in bioavailability and the absorption profiles: a new dose titration must be carried out. This may result in insufficient pain control during the titration phase.

#### Health economics

• No analyses identified.

#### Costs

- The costs for one dose of the fentanyl products (regardless of strength) are: Abstral sublingual tablet £4.99, Actiq lozenge  $\pounds$ 6.20 and Effentora buccal tablet  $\pounds$ 5.14.
- 100mLs of morphine oral solution (2mg/mL) costs £1.87.

#### Issues for consideration

- No more than 4 episodes of breakthrough pain a day should be treated with an immediate-release fentanyl preparation.
- The fixed dose of strong opioid to control the cancer-related pain should be reviewed and adjusted frequently to ensure that breakthrough pain episodes and the use of immediate-release products are kept to a minimum.
- Intranasal fentanyl reaches maximal plasma concentrations faster than the other preparations and the mean pain intensity difference from baseline seen compared to placebo, is greater than that achieved with the other products. All of the immediate release fentanyl preparations provide adequate pain relief within 10-15 minutes, when compared to placebo, albeit to varying degrees.
- There is potential for prescribing and dispensing errors if more than one formulation is available locally or prescribed in the community, as the strengths are similar. In order to prevent such errors, ensure that the brand name of the correct product is on the prescription.
- Experience with palliative care patients has found that Effentora takes longer to dissolve than Abstral, feels uncomfortable and can leave a prolonged taste. Patients tend to prefer Abstral and Actiq to Effentora.
- Re-dosing with any of the immediate-release products should not be done within at least 4 hours of the previous dose. There are no specific guidelines on how to change from one product to another, but based on how often a dose can be taken, it could be assumed that a different preparation should not be used within 4 hours of the original one.

#### Background

Immediate-release (IR) fentanyl is used to treat breakthrough pain, a transient exacerbation of otherwise controlled chronic background pain.<sup>1</sup> Breakthrough pain has been estimated to affect 50-90% of patients with cancer<sup>2</sup> and can be predictable (related to movement or activity such as swallowing and coughing) or spontaneous.<sup>3</sup> The aim of this review is to evaluate the currently available IR fentanyl preparations (Abstral sublingual tablets, Actig lozenges and Effentora buccal tablets) plus the newly licensed intranasal formulation (Instanyl), and to discuss whether the products are interchangeable and when it is most appropriate to use each one. The review will not discuss the analgesic efficacy of fentanyl per se, as this is well established, or the use of strong opioids in palliative care, but will evaluate studies that compare the different fentanyl IR products.

Reviews on the use of strong opioids in palliative care, including the use of fentanyl lozenges, can be found at: <u>http://</u> <u>www.npc.co.uk/ebt/merec/pain/otherback/</u> <u>resources/merec\_briefing\_no22.pdf</u> and at <u>http://www.nyrdtc.nhs.uk/docs/dud/</u> <u>DU\_63\_OPIOID.pdf</u>.

A review on fentanyl buccal tablets can be found at: <u>http://www.nelm.nhs.uk/en/NeLM-</u> <u>Area/Evidence/Drug-Specific-Reviews/</u> <u>Fentanyl-buccal-tablets/</u>. There are four fentanyl products licensed to treat breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain:

- Sublingual tablets (Abstral)
- Buccal lozenges (Actiq)
- Buccal tablets (Effentora)
- Intranasal spray (Instanyl)

Abstral, Actiq and Effentora have already been launched in the  $UK^{1;4;5}$ ; Instanyl was approved for use in the EU in April 2009<sup>6</sup> and is due to be launched Q3 2009<sup>7</sup>.

The Scottish Medicines Consortium has made recommendations for the use of Effentora and Abstral® within NHS Scotland:

- Both fentanyl buccal tablets (Effentora) and fentanyl sublingual tablets (Abstral) are accepted for restricted use within NHS Scotland for treating breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.<sup>8;9</sup>
- Use of Abstral® should be restricted to patients who are unsuitable for any other short-acting opioid, such as oral morphine. Abstral® offers an alternative to buccal administration at a reduced cost.<sup>9</sup>

## Dose and administration

Each fentanyl product should be titrated to the most effective dose that provides adequate analgesia and minimises side effects. Switching from one product to another must not be done at a 1:1 ratio due to differences in bioavailability and the absorption profiles: a new dose titration must be carried out.<sup>1;4</sup> Switching between products may cause a delay in patient benefit, causing unnecessary pain.

Doses, administration methods and pharmacokinetics are detailed in table 1.

# Other treatments for breakthrough cancer pain

It is common to give an extra dose of the patient's regular analgesic for breakthrough pain. For example, morphine can be prescribed, either as an oral solution or standard formulation tablets. Various dosing regimens have been used, e.g. 1) The morphine dose should be approximately one-sixth of the total daily dose of oral morphine, repeated every 4 hours as necessary.<sup>10</sup> This approach effectively doubles the patient's morphine intake for the next 4 hours.<sup>3</sup> 2) The dose should be ~10% of the total regular daily dose. The intensity of breakthrough pain episodes can vary so the optimised dose can range from 5-20%.<sup>3</sup>

Zeppetella<sup>11</sup> carried out a prospective survey of hospice admissions of 50 patients with breakthrough pain to compare patient assessments of time to relief among the various immediate release opioids prescribed. These were morphine (n=10), oxycodone (n=10), hydromorphone (n=10), methadone (n=10) or transmucosal fentanyl citrate (OTFC) (n=10). Patients were asked to determine the speed of effectiveness of their rescue medication using an 11 point scale (0=no relief, 10=complete relief). The average number of breakthrough pain episodes a day was 4 (range 1-8) and 50 episodes were assessed for each medication (total 250). No difference in effectiveness was seen among the oral opioids (score 6.2-6.7). OTFC was rated more effective than morphine, oxycodone and hydromorphone (p<0.01) and methadone (p=0.045) (score 8.1). This may be because the dose of the oral rescue opioid was ~18% of the total daily regular dose,

compared with the OTFC does which was  $\sim$ 36% of the total daily regular dose. The average time to meaningful pain relief was 31 minutes (range 5-75). No difference was found between morphine, hydromorphone and oxycodone. Methadone was found to work faster than morphine (p<0.01) whilst OFTC worked faster than all other 4 medications (p<0.001).

In this survey it was found that most breakthrough pain episodes lasted an average of 35 minutes, and oral rescue medication took 30-40 minutes to produce an effect. Therefore, the pain episode may be over by the time the analgesic is effective. Ideally the medication used to treat breakthrough pain should have a faster onset of action.

# Patients with xerostomia/dry mouth or mucositis

Patients with a dry mouth are advised to moisten the buccal cavity before administration of Effentora, Actiq or Abstral<sup>1;4;5</sup>; if this does not help then switching to another product is advised. Morphine sulphate oral solution may be a suitable alternative.

The use of Abstral has not been studied in patients with mucositis or mouth wounds.<sup>1</sup> There may be a risk of increased systemic drug exposure and therefore extra caution is required during dose titration.<sup>1</sup> Differences in exposure with Effentora have been shown in a clinical study in patients with grade 1 mucositis; the differences were not clinically significant.<sup>4</sup> There is little information regarding the use of Actig lozenges in patients with mucositis: results from a small pilot study of patients with grade 3/4 mucositis showed that the lozenges were well tolerated but could cause a mild burning sensation.12 If signs of excessive opioid effects appear before the whole lozenge is consumed, it should be removed and consideration given to decreasing future doses.<sup>5</sup>

products
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Table 1:

Broduct	Deciform	Administration	Dharmacolinotics
Abstral <sup>1</sup>	Sublingual tablets Sublingual tablets 100mcg, 200mcg, 300mcg, 400mcg, 600mcg, 800mcg. Optimal dose determined by upward titration, start- ing with 100mcg and ti- trating upwards as neces- sary through the range of available dosage strengths.	<ul> <li>Administer directly under the tongue at the deepest part. Do not swallow but allow to dissolve completely in the sublingual cavity without chewing or sucking. Do not eat or drink until the tablet is completely dissolved.</li> <li>Patients with a dry mouth can use water to moisten the buccal mucosa before using Abstral.</li> <li>Maximum 4 doses a day; re-evaluate longaction opioid dose if &gt;4 required for 4 or more consecutive days.</li> </ul>	<ul> <li>Rapid absorption of fentanyl occurs over about 30 minutes.</li> <li>Bioavailability is estimated at ~70%.</li> <li>Mean maximal plasma concentrations of 0.2-1.3ng/mL (after taking 100 to 800mcg) are reached within 22.5-240 minutes.</li> <li>Pain relief seen within 15 minutes post-dose.*</li> </ul>
Actiq <sup>5</sup>	<b>Oromucosal lozenges</b> 200mcg, 400mcg, 600mcg, 800mcg, 1200mcg, 1600mcg. Optimal dose determined by upward titration, start- ing with 200mcg and ti- trating upwards as neces- sary through the range of available dosage strengths.	<ul> <li>Place the lozenge in the mouth against the cheek and move around using the applicator, with the aim of maximising the amount of mucosal exposure to the product. Suck but don't chew the lozenge. The lozenge should be consumed within 15 minutes.</li> <li>Patients with a dry mouth can use water to moisten the buccal mucosa before using Actig.</li> <li>Maximum 4 doses a day; re-evaluate longaction opioid dose if &gt;4 required for 4 or more consecutive days.</li> </ul>	<ul> <li>25% of the dose is absorbed from the buccal muscosa; 75% is swallowed and absorbed via the gastrointestinal tract (GIT).</li> <li>Absolute bioavailability is ~50%, once hepatic and intestinal first-pass metabolism is taken into consideration.</li> <li>Mean maximal plasma concentrations of 0.39 to 2.51ng/mL (after taking 200 to 1600mcg) are around 20-40 minutes (range 20-480 minutes) post dose.</li> <li>Pain relief seen within 15 minutes post-dose.*</li> </ul>
Effentora <sup>4</sup>	<b>Buccal tablets</b> 100mcg, 200mcg, 400mcg, 600mcg, 800mcg Optimal dose determined by upward titration, start- ing with 100mcg and ti- trating upwards as neces- sary through the range of available dosage strengths	<ul> <li>Place the tablet in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum). Keep in place long enough to allow disintegration of the tablet, usually 14-25 minutes. Do not suck, chew or swallow the tablet. Any tablet remaining after 30 minutes can be swallowed with a glass of water.</li> <li>Wait at least 4 hours before treating another BTP episode. Re-evaluate long-action opioid dose if &gt;4 doses/day required.</li> </ul>	<ul> <li>Approximately 50% of the dose is absorbed transmucosally. 50% is swallowed and absorbed slowly from the GIT, with ~30% of the swallowed dose escaping hepatic and intestinal first-pass elimination.</li> <li>Absolute bioavailability is 65%.</li> <li>Mean maximal plasma concentrations of 0.6 to 1.44ng/nL are reached in 46.8 minutes (range 20-240).</li> <li>Pain relief seen within 10 minutes post-dose.*</li> </ul>
Instanyl <sup>13</sup>	Nasal spray 50mcg, 100mcg, 200mcg. Optimal dose determined by upward titration, start- ing with 50mcg and titrat- ing upwards as necessary through the range of avail- able doses.	<ul> <li>Administer one puff in one nostril. A second dose of the same strength can be administered in the other nostril<sup>7</sup> at least 10 minutes later if the first dose does not give adequate analgesia. Patients should sit or stand in the upright position when administering.</li> <li>Maximum treatment = 4 BTP episode a day, treated at least 4 hours apart. Re-evaluate long-action opioid dose if &gt;4 doses/day required.</li> </ul>	<ul> <li>Absolute bioavailability is 89%.</li> <li>Maximal plasma concentrations of 0.35-1.2ng/mL reached within 12-15 minutes from 50-200mcg doses.</li> <li>Median time to onset of meaningful pain relief is 7 minutes (max 11 minutes)<sup>7</sup></li> <li>Duration of analgesic effect is 56 minutes.</li> <li>Nasal route avoids first-pass metabolism.<sup>6</sup></li> <li>Pain relief seen within 10 minutes post-dose.*</li> </ul>

#### Clinical efficacy – comparator trials

No trials comparing fentanyl products for breakthrough cancer pain were identified. Trials comparing intranasal fentanyl with Actiq lozenges are in progress.<sup>7</sup>

## Mixed-treatment comparison

Stam et al<sup>14</sup> compared the efficacy of fentanyl buccal tablets (FBT), oromucosal fentanyl citrate (OTFC), intranasal fentanyl (INFS) and morphine sulphate immediate release (MSIR) in a 'Bayesian mixed treatment comparison' (MTC). A MTC is an extension of a traditional meta-analysis that allows comparisons of relative efficacy in the absence of head-tohead trials. The Bayesian approach is considered the method of choice because direct probability statements can be made.<sup>15</sup>

The MTC inclusion criteria were: randomised, controlled trials, oral or nasal administration of fentanyl and adult cancer patients with breakthrough pain. Outcomes were pain intensity difference (PID) at the start of a BTP episode and at the time points reported for up to 60 minutes. Pain intensity was measured on an 11-point scale: 0=no pain, 10=worst pain.<sup>2;16;17</sup> The primary outcome of analysis was the PID between treatments estimated for the first 30 minutes. The PID was recorded at different time points for the individual interventions: at 10, 20 and 40 minutes for INFS and at 15, 30 and 45 minutes for FBT and OTFC.

Five trials met the inclusion criteria: four placebo-controlled trials of OFTC, FBT and INFS, plus one trial comparing OFTC with MSIR. All studies started with an open-label titration

2.09 (1.58, 2.60)

phase followed by a double-blind, randomised treatment phase.

All fentanyl treatments were more effective than placebo in treating breakthrough pain at all time points. OFTC was more effective than MSIR in treating breakthrough pain at all time points. Intranasal fentanyl provided a greater reduction in pain at 10 minutes compared to that provide by the buccal tablets and oromucosal lozenges at 15 minutes (see table 2). The superior pain reduction achieved with the intranasal spray compared with the other interventions was maintained for up to 45 minutes after administration.

There are limitations to using a mixed treatment comparison. Randomisation can differ across the trials, therefore study design and patient characteristics may also differ. An indirect comparison can therefore be biased, though the Stam et al state that as the studies included in this MTC were similar with regard to patient characteristics and design (see table 3), they do not expect bias to be a great concern. One difference between the oromucosal and buccal trials was if the breakthrough pain was not adequately controlled by the fentanyl product used, a second oromucosal dose could be used but a second buccal dose could not (instead the patient took a dose of pre-study supplemental medication). Morphine solution would have been a better comparator for the OTFC/MSIR trial, as it is absorbed faster than the tablets (time to maximum concentration is 50 min vs. 70-80mins for solution and tablets respectively). No actual figures for pain relief were published in this OTFC/MSIR comparison study.<sup>3</sup> The trial for the intranasal preparation has not been published.

Mean Pain intensity difference (95% CI)	Intranasal	Buccal	Oromucosal	Morphine sulphate
10 mins	1.28 (0.91, 1.65)			
15 mins		0.51 (0.29, 0.79)	0.60 (0.11, 1.09)	0.18 (-0.5, 0.86)
20 mins	1.90 (1.42, 2.39)			

0.96 (0.62, 1.30)

1.41 (1.07, 1.75)

Table 2: Treatment effects (pain intensity difference) relative to placebo

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30 mins

40 mins

45 mins

0.41 (-0.35,

0.48 (-0.47,

1.17)

1.42)

0.90 (.030, 1.50)

0.97 (0.16, 1.78)

Table 3: Individual trial details (no published details for the intranasal trial)

	Buccal tablets <sup>2</sup>	Buccal tablets <sup>17</sup>	Orotransmucosal <sup>16</sup>	Morphine sulphate
Patients	≥18 years of age	18-80 years of age	$\geq$ 18 years of age (n=93)	Adults (n=89)
Regular pain medication	Oral morphine 60- 1000mg/day, or equivalent, or 50- 300mcg/hour transdermal fentanyl for at least 1 week	At least 60mg/day oral morphine or 25mcg/hr transdermal fentanyl, or equivalent for at least 1 week.	At least 60mg/day oral morphine or 50mcg/hr transdermal fentanyl or equivalent.	Oral morphine 60- 1000mg/day, or equivalent, or 50- 300mcg/hour transdermal fentanyl, plus successful dose of MSIR (15-60mg).
Breakthrough episodes a day	1-4	1-4	At least 1	1-4
Type of cancer	Solid or haematologic malignancy and an Eastern Cooperative Oncology Group (ECOG) performance status rating of ≤2.	Solid or haematologic malignancy.	All types and stages.	All types and stages.
Life expectancy	≥3 months	At least 2 months	Not stated	Not stated.
Titration phase (open label)	Yes, to effective dose.	Yes, to effective dose.	Yes, to effective dose.	Yes, to effective OTFC dose.
Treatment	Random assignment to 1 of 18 pre- specified dose sequences of 10 tablets (7 active and 3 placebo), all of which had to be taken within a 21-day period, with a maximum of 4 episodes treated each day). Prestudy supplemental medicines could be taken if adequate pain relief not achieved within 30 mins.	Random assignment to 1 of 18 pre- specified dose sequences of 10 tablets (7 active and 3 placebo), all of which had to be taken within a 21-day period, with a maximum of 4 episodes treated each day. Prestudy supplemental medicines could be taken if adequate pain relief not achieved within 30 mins.	10 period crossover: 10 sequentially numbered units (7 active and 3 placebo) to be taken in the designated order. Second dose could be taken after 30 mins if first not effective enough.	10 prenumbered sets of OTFC/placebo MSIR and placebo OTFC/MSIR, to be taken by a randomised order. No additional medications allowed for 1 hour post-study medication. New episodes could be treated after 2 hours had elapsed. Mean MSIR dose: 31±13.5mg Mean OTFC dose: 811±452mcg.
Pain intensity measured at <sup>†</sup>	15, 30, 45 and 60 mins post dose.	5, 10, 15, 30. 45, 60, 90, 120 mins post dose.	15, 30, 45 and 60 mins post dose.	15, 30, 45 and 60 mins post dose.
Pain intensity difference (active – placebo)*	30 mins: 1.2	10 mins: 0.4 60 mins: 4.8	15 mins: 0.60 30 mins: 0.90 45 mins: 0.97 60 mins: 1.06	At each time point mean PID favoured OTFC over MSIR (p<0.008). Pain relief was significantly aroater with OTFC then
Pain intensity difference (active – placebo) ITT population*	Not stated	Not stated	15 mins: 0.58 30 mins: 0.87 45 mins: 0.63 60 mins: 0.66	MSIR at all time points ( $p \le 0.009$ ). Note that no numerical data were presented and therefore PIDs cannot be compared. >33% change in PID seen in 42.3% of episodes treated with OTFC and 31.8% of episodes treated with MSIR ( $p=0.001$ ).
† 11 point scale (0=no pain, 10=worst pain)				

#### Costs

**Abstral** Tablets (sublingual)<sup>19</sup> 10x100mcg, 200mcg, 300mcg, or 400mcg = £49.99; (1 tablet = £4.99) 30x100mcg, 200mcg, 300mcg, 400mcg, 600mcg or 800mcg = £149.70. (1 tablet = £4.99)

Actiq Lozenge (buccal)<sup>10</sup>, with oromucosal applicator: 3x200mcg, 400mcg, 600mcg, 800mcg, 1200mcg or 1600mcg = £18.58; (1 lozenge = £6.20) 30x2000mcg, 400mcg, 600mcg, 800mcg, 1200mcg or 1600mcg = £185.80 (1 lozenge = £6.20)

Effentora buccal tablets<sup>20</sup>: 4x100mcg, 200mcg, 400mcg, 600mcg or 800mcg= £20.56 (1 tablet = £5.14)

**Oromorph** (morphine oral solution)<sup>10</sup> 10mg/5mL (2mg/mL): 100mL =  $\pounds$ 1.87; 300mL =  $\pounds$ 5.21; 500mL =  $\pounds$  7.86.

Sevredol (morphine sulphate immediate release tablets)<sup>10</sup>  $56x10mg = \pounds 5.61 (1 \text{ tablet} = 10p)$   $56x20mg = \pounds 11.21 (1 \text{ tablet} = 20p)$  $56x50mg = \pounds 28.02 (I \text{ tablet} = 50p)$ 

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**Embase**: [FENTANYL CITRATE/bd,na,li [bd=Buccal Drug Administration, na=Intranasal Drug Administration, li=Sublingual Drug Administration] or [FENTANYL/bd,na,li [bd=Buccal Drug Administration, na=Intranasal Drug Administration, li=Sublingual Drug Administration]] and [CANCER PAIN/dt [Drug Therapy]]

**Embase:** [FENTANYL CITRATE/bd,na,li [bd=Buccal Drug Administration, na=Intranasal Drug Administration, li=Sublingual Drug Administration] or [FENTANYL/bd,na,li [bd=Buccal Drug Administration, na=Intranasal Drug Administration, li=Sublingual Drug Administration]] and HEALTH ECO-NOMICS/.

**Embase:** \*FENTANYL/ OR \*FENTANYL CITRATE/ and MUCOSA INFLAMMATION/co [co=Complication]

**Medline**: FENTANYL/ad,tu [ad=Administration & Dosage, tu=Therapeutic Use] [Limit to: Humans and English Language] and \*PAIN/dt [Drug Therapy]. FENTANYL/ad,tu [ad=Administration & Dosage, tu=Therapeutic Use] [Limit to: Humans and English Language] and PALLIATIVE CARE/mt [Methods]

**Medline**: exp FENTANYL/ and ECONOMICS, PHARMACEUTICAL/ **Medline**: MUCOSITIS/ and exp FENTANYL/

IDIS: ["FENTANYL 28080810" and breakthrough]] IDIS: "FENTANYL 28080810" and Descriptor(s): "ECON DRUG ECONOMICS 129" or "ECON COST BENEFIT 130" or "ECON COST EFFECTIVENESS 131" IDIS: ("FENTANYL 28080810" or "FENTANYL DERIVATIVES 94000129") and "MORPHINE 28080819" and Disease(s): "PAIN, NEOPLASM RELATED 338.3"; breakthrough and Drug(s): ("FENTANYL 28080810" or "FENTANYL DERIVATIVES 94000129") and "MORPHINE 28080819"