

# NEW DRUG EVALUATION

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## INTRANASAL FENTANYL

**Instanyl<sup>®</sup>▼ is a new preparation that delivers the strong opioid fentanyl as an intranasal spray. It appears to have superior analgesic efficacy to placebo, and a faster onset of relief of breakthrough pain associated with cancer than fentanyl lozenges (Actiq<sup>®</sup>), although the evidence is of low quality. No unexpected safety concerns were identified in clinical studies, however the initiation, titration, and maintenance instructions are complex and this may present a risk for error. Instanyl<sup>®</sup>▼ is costly compared with other strong opioid preparations and is therefore unlikely to represent a cost-effective treatment option.**

### What is it?

Fentanyl is a strong opioid analgesic available as transdermal patches, buccal tablets, sublingual tablets, oromucosal lozenges, and solution for injection.<sup>1,2</sup> Instanyl<sup>®</sup>▼ (Nycomed) is a novel intranasal spray resulting in absorption of fentanyl into the systemic circulation via the nasal mucosa.<sup>3</sup> It is licensed for the treatment of breakthrough pain in adults already receiving opioid maintenance therapy for chronic cancer pain. The recommended dose is one spray when required.<sup>3</sup> If analgesia is insufficient a second spray can be administered via the other nostril at least 10 minutes after the first spray. No more than two sprays should be administered per episode of pain, and Instanyl<sup>®</sup>▼ should not be used more frequently than four hourly with a maximum eight sprays daily.<sup>3</sup>

Instanyl<sup>®</sup>▼ is available in 10- or 20-dose bottles, each delivering 50, 100 or 200 micrograms per spray.<sup>4</sup>

### How effective is it?

The European Medicines Agency (EMA) Public Assessment Report (EPAR) refers to three main efficacy studies<sup>5</sup> of which two have been published in full.<sup>6,7</sup> The studies were conducted in patients with cancer associated pain experiencing  $\geq 3$  episodes of breakthrough pain per week despite use of background opioid analgesics.<sup>5-7</sup>

The first study consisted of a dose-titration phase, a double-blind placebo-controlled efficacy phase (n = 113) and a 10-month follow-up phase to assess safety and tolerability (n = 108).<sup>6</sup> During the efficacy phase patients received eight doses consisting of two placebo and six fixed Instanyl<sup>®</sup>▼ doses in a random sequence. The primary outcome measure was the difference in pain intensity score (range 0 to 10) between baseline and 10 minutes after first administration. At 10 minutes Instanyl<sup>®</sup>▼ demonstrated a greater reduction in pain intensity score than placebo (mean difference of 1.26 units, p < 0.001).<sup>6</sup>

An earlier study reported in the EPAR was of similar design (n = 152) but with patients receiving two doses of each fentanyl strength and placebo in a random order.<sup>5</sup> The mean difference in pain intensity score after 10 minutes

compared with placebo was 0.41, 0.81 and 1.24 units with Instanyl<sup>®</sup>▼ 50, 100 and 200 micrograms respectively (p < 0.001 for each vs. placebo).<sup>5</sup>

The EMA identified serious problems with conduct at two study centres involved in both studies, making the overall results unreliable.<sup>5</sup> Results reported in this review are adjusted to exclude potentially erroneous data.

The minimum clinically important change on the 11-point numerical rating scale is considered to be 1.4 points. Instanyl<sup>®</sup>▼ did not consistently meet this level in placebo-controlled studies.<sup>8</sup>

The third study was an open-label, randomised, crossover comparison with fentanyl oromucosal lozenges (Actiq<sup>®</sup>) in 139 patients.<sup>7</sup> This demonstrated a faster onset of pain relief with Instanyl<sup>®</sup>▼ than Actiq<sup>®</sup> (median time to onset of 'meaningful pain relief' 11 vs. 16 minutes).

Almost half of the patients in these studies required the maximum dose of 200 micrograms per actuation,<sup>6</sup> and about two-thirds used two actuations per episode regardless of the preparation strength.<sup>5</sup>

### How safe is it?

Fentanyl is about 70 to 150 times more potent than morphine and has been the subject of recent safety warnings.<sup>2,9</sup> No unexpected safety issues arose in the clinical studies of Instanyl<sup>®</sup>▼ and adverse effects were typical of a strong opioid, e.g. nausea, vomiting, dizziness and constipation.<sup>3</sup> Test doses were used to identify patients unable to tolerate a single maximal dose of Instanyl<sup>®</sup>▼ which may lead to underestimation of adverse effects.

In the published placebo study, including data from the open-label phase with follow-up of ten months, the most common adverse effects were nausea (13%), constipation (10%), asthenia (9%), vertigo (8%) and vomiting (7%).<sup>6</sup>

In the crossover study the most common adverse effects during the Instanyl<sup>®</sup>▼ phase were nausea (8%), vomiting (5%), and constipation (4%), which also affected 8%, 3% and 3% of patients, respectively, during the Actiq<sup>®</sup> phase.<sup>7</sup>

Across all studies there was one report of nasal ulceration which rapidly healed following cessation of therapy<sup>7</sup> and one report of a nose bleed.<sup>6</sup>

All suspected adverse reactions to black triangle drugs such as Instanyl<sup>®</sup> should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

Numerous other strong opioid analgesics are used to manage breakthrough pain, for example morphine oral solution is widely used, well understood, and inexpensive. Instanyl<sup>®</sup> has not been compared with morphine oral solution. More costly options include immediate-release formulations of morphine tablets, oxycodone capsules and solution, hydromorphone capsules, and other fentanyl

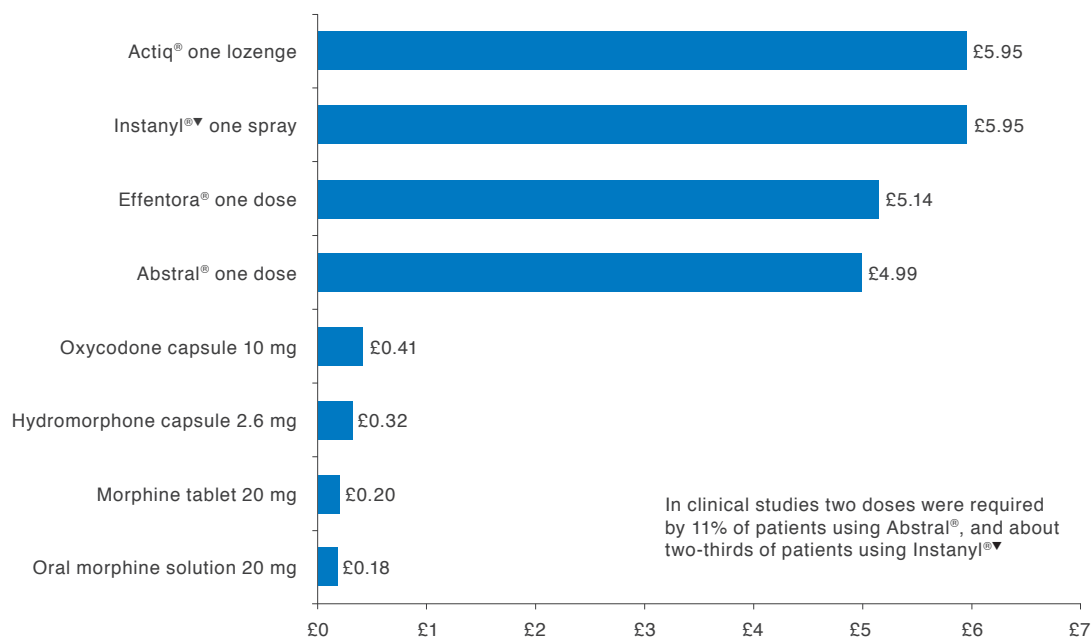
preparations such as buccal tablets, sublingual tablets, and oromucosal lozenges.<sup>1,2</sup> There is a paucity of good evidence to indicate superiority of one drug or formulation over another,<sup>10</sup> but at typical doses and frequencies Instanyl<sup>®</sup> is one of the most costly options.

### When should it be used?

Due to complex initiation and titration requirements, relatively complicated user instructions and lack of proven advantages over less costly options, Instanyl<sup>®</sup> is not generally recommended for the treatment of pain for palliative care. Any use should only be initiated by specialists when more cost-effective options are unsuitable. Instanyl<sup>®</sup> is not appropriate for use in general practice.

### How much does it cost?

Cost to treat a single episode of breakthrough pain (NHS dm+d December 2009)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. (ADQ) values are used where available.

## REFERENCES

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KEY R - review RCT - randomised controlled trial.

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