

# Instanyl: intranasal fentanyl for treating breakthrough pain

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## KEY POINTS

- Instanyl is an intranasal formulation of fentanyl for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain
- the recommended dose is one spray of 50, 100 or 200µg, repeated after 10 minutes if necessary and treating up to 4 pain episodes per day; 10 doses = £59.50, 20 doses = £119.00 for all formulations
- in clinical trials, 30-60 per cent of patients obtained significant pain relief after 10 minutes but most required 2 doses
- in one trial, Instanyl relieved pain faster than Actiq and maintained superior analgesia for 1 hour
- the adverse effects associated with Instanyl are comparable with those of other fentanyl formulations
- intranasal delivery offers an opportunity for rapid opioid absorption and, together with a lipophilic drug such as fentanyl, is more suited to the temporal features of breakthrough pain



**Instanyl is an intranasal formulation of fentanyl licensed for breakthrough pain management in chronic cancer pain. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects and Dr Giovambattista Zeppetella discusses its place in the management of breakthrough pain.**

**B**reakthrough pain – transient flares of pain in a patient with otherwise controlled pain<sup>1</sup> – is typically of moderate-to-severe intensity and peaks within three minutes; it is often of short duration (median 30 minutes).<sup>2</sup> It may be provoked by a movement or procedure and therefore can be anticipated (incident) or it may be unexpected (spontaneous).

Breakthrough pain is associated with worse psychological and social outcomes and reduced quality of life.<sup>1</sup> In one study, hospice patients with cancer reported an average of four episodes of breakthrough pain per day.<sup>4</sup>

A recent consensus statement on the management of cancer-related breakthrough pain stated that opioids are the treatments of choice but

recommended no specific products.<sup>1</sup> Although oral immediate-release formulations of morphine are widely used, they do not have a sufficiently rapid onset of action and their duration of action is too long.<sup>1</sup>

Alternatives that may act more quickly include fentanyl sublingual tablets (Abstral), oral transmucosal lozenges (Actiq) and buccal tablets (Effentora). The fentanyl lozenge has been shown to offer superior analgesia to oral morphine in patients with breakthrough pain.<sup>3</sup>

### The technology

Instanyl is a nasal spray delivering 50, 100 and 200µg fentanyl per actuation. It is licensed for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain.

Up to four breakthrough pain episodes may be treated daily, each with no more than two doses separated by at least 10 minutes. There should be an interval of at least four hours before treating another breakthrough pain episode.

The initial dose is 50µg, repeated after 10 minutes if necessary; if analgesia is inadequate, a higher dose should be considered for the next episode.

Maintenance opioid therapy is defined as at least 60mg oral morphine daily, at least 25µg transdermal fentanyl per hour, at least 30mg oxycodone daily, at least 8mg oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Instanyl is contraindicated in opioid-naïve patients, patients with

severe respiratory depression or severe obstructive lung conditions, previous facial radiotherapy or recurrent epistaxis.

It should be used with caution in older people, patients with moderate-to-severe renal or hepatic impairment, respiratory depression or obstructive lung disease, raised intracranial pressure, bradyarrhythmias or hypotonia and/or hypovolaemia.

Fentanyl shares the drug interactions of other opioids. Dose adjustment is not required in patients with the common cold but nasal vasoconstrictors, *eg* oxymetazoline, should be avoided. Alternative routes of administration should be sought for other drugs administered intranasally.

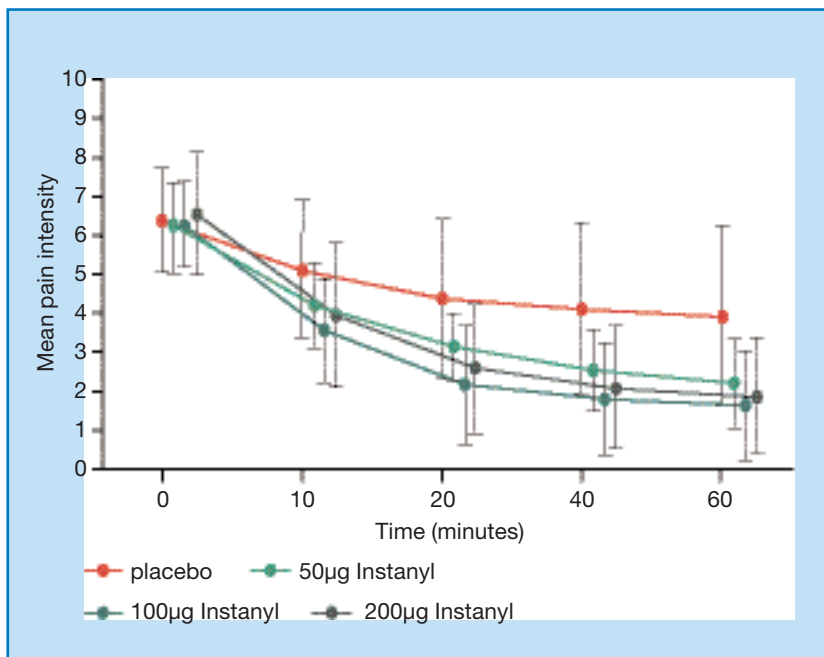
### Clinical trials

Two phase III trials,<sup>5,6</sup> one currently unpublished,<sup>5</sup> provide the key efficacy data for Instanyl. Opioids and other analgesics were continued. One comparative trial with Actiq has also been published.<sup>7</sup>

The first trial<sup>5</sup> was a dose-ranging study including 159 patients with cancer pain and stable background analgesia with an opioid (mean dose 192µg per day oral morphine equivalent) but who were experiencing between three episodes of breakthrough pain per week and four per day. Patients who could not tolerate a single test dose of 200µg Instanyl were excluded.

Two pain episodes were each treated with placebo or 50, 100 or 200µg Instanyl in random order, with a repeat dose after 10 minutes if analgesia was insufficient; only one episode per day was treated.

The primary end-points were the pain intensity difference between predose and 10 minutes postdose scores on a numerical rating scale (PID10) and average



**Figure 1.** Mean reduction in pain intensity with placebo and optimal Instanyl dose after 10, 20, 40 and 60 minutes (after ref 5)

responder rates for two episodes (response defined as PID10 >2).

Instanyl dose-dependently improved PID10 significantly compared with placebo; mean responder rates were 29, 42 and 50 per cent for 50, 100 and 200µg doses compared with 22 per cent with placebo.

The proportions of patients who needed a second dose after 10 minutes (averaged over the first two episodes) were 75, 70 and 58 per cent respectively for Instanyl and 78 per cent for placebo.

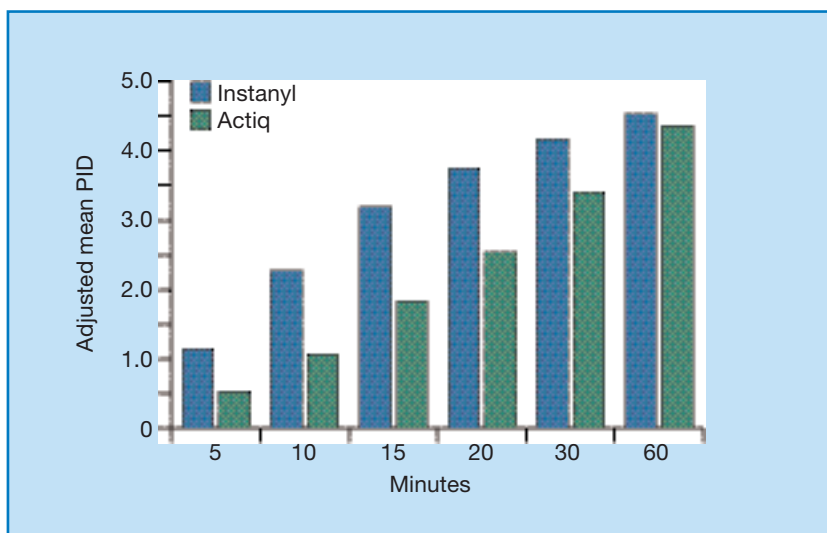
In the second trial,<sup>6</sup> 120 patients from two previous trials of Instanyl<sup>5</sup> underwent dose titration of Instanyl (using the licensed procedure) and then, double blind and in random order, used the optimal dose (repeated if necessary) to treat six pain episodes and placebo to treat two episodes over a period of three weeks. The proportions taking each dose of Instanyl were: 50µg, 15 per cent; 100µg, 46 per cent; 200µg, 39 per cent. They then entered a non-blinded 10-month phase to assess

safety. The primary end-points were those of the first trial.

All doses of Instanyl significantly improved PID10 compared with placebo after 10, 20, 40 and 60 minutes (see Figure 1) and reduced the use of rescue medication (1-2 per cent of patients at 10-20 minutes compared with 17 per cent with placebo).<sup>6</sup> Responder rates at 10 minutes were 21 per cent with placebo and 31, 60 and 49 per cent for increasing doses of Instanyl.<sup>5</sup>

The proportions of episodes requiring two doses were 84 per cent for placebo and 69, 62 and 76 per cent for Instanyl.<sup>5</sup> Overall, 75 per cent of patients rated Instanyl as good or excellent compared with 31 per cent with placebo.<sup>6</sup>

The comparative study<sup>7</sup> was a crossover trial with similar recruitment criteria in which 139 patients were randomised to dose titration and treatment of six episodes over two weeks with Instanyl 50, 100 or 200µg (up to two doses) or Actiq 200-1600µg. The primary end-point was the time to onset of



**Figure 2.** Pain intensity difference (PID) over 60 minutes after administration of Instanyl and Actiq (after ref 7)

meaningful pain relief, as defined by the patient.

Fifty-three patients (28 per cent) withdrew from the trial during the titration and efficacy phases, due to adverse effects in 17 (12 per cent). The median time to onset of meaningful pain relief was 11 minutes with Instanyl and 16 minutes with Actiq; approximately two-thirds of patients obtained faster pain relief with intranasal administration. PID10 was signifi-

cantly improved after intranasal administration and this was maintained for up to one hour (see Figure 2).

#### Adverse effects

The adverse effects associated with Instanyl are typical of other fentanyl formulations.<sup>5</sup> During the non-blinded safety phase of the second trial, 36 per cent of patients discontinued treatment due to adverse events.<sup>5</sup> In the comparative trial,

adverse events were reported by 46 per cent of patients after intranasal administration and by 35 per cent after Actiq.<sup>7</sup> The commonest adverse events were nausea (8 per cent), vomiting (4-5 per cent) and constipation (3-4 per cent); numbers of other adverse events were too low for comparison.

#### References

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## Place in therapy

Breakthrough pain in cancer patients is increasingly recognised as an important and challenging clinical problem. Oral opioids, although commonly used, often provide partially effective treatment; hence, in an effort to deliver more effective treatment, trans-mucosal opioids have been developed.

In the UK there are currently four trans-mucosal formulations, all containing fentanyl, of which Instanyl is the only one administered nasally. Intranasal delivery offers a unique opportunity for rapid opioid absorption that, together with a lipophilic drug such as fentanyl, is

more suited to the temporal features of breakthrough pain.

The evidence outlined above suggests that Instanyl may have an important role in the management of breakthrough cancer pain as illustrated by pharmacokinetic and clinical efficacy studies. Not only has Instanyl been shown to be well tolerated and to provide pain relief within 10 minutes of administration, but in the open-label comparative study Instanyl was superior to Actiq.

Furthermore, compared to other trans-mucosal formulations, it may be advantageous for xerostomia, which is common in patients with advanced malignant disease.

Use of Instanyl should be considered in patients where normal-release morphine is unsuitable and as an alternative to other buccal and sublingual fentanyl preparations.

In common with oral trans-mucosal formulations, the successful dose of Instanyl cannot be predicted from the patient's around-the-clock analgesia. Titration of rescue medication is therefore required; furthermore, titration schedules vary from one product to another, so patients switching to Instanyl may require retitration.

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