Abstral®
SUBLINGUAL FENTANYL TABLET

Medicines evidence pack to support decision taking for formulary inclusion

Abstral® (fentanyl citrate) is indicated for the management of breakthrough pain (BTcP) in adult patients using opioid therapy for chronic cancer pain.[1]

FOR THE UNITED KINGDOM: Adverse Events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk. Adverse Events should also be reported to Kyowa Kirin Ltd. on +44 (0)1896 664000, email medinfo@kyowakirin.com

FOR THE REPUBLIC OF IRELAND: Adverse Events should be reported. Information about adverse event reporting can be found at www.hpra.ie. Adverse Events should also be reported to Kyowa Kirin Ltd. on +44 (0)1896 664000, email medinfo@kyowakirin.com

RESPONSIBLE USAGE

Abstral® (fentanyl (as citrate)) is indicated for the management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Please note not all medicines containing opioids are authorised for all types of pain indication. Refer to the Summary of Product Characteristics before prescribing. Scan the QR code for advice on the responsible use of opioids, including those indicated for other types of pain.

Grünenthal Meds

Prescribing information is available at the end of this document

Contents

Abstral® overview[1,2]

1

Brand name	Abstral®
Generic name	Fentanyl citrate
Pharmaceutical form	Sublingual tablet
Indication	Management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain
BNF class	Central nervous system: Analgesics: Opioid analgesics
Posology	Abstral® is only to be prescribed to patients considered to be tolerant to their opioid therapy for persistent cancer pain. Patients can be considered tolerant if they have taken at least 60mg of oral morphine daily, at least 25mcg of transdermal fentanyl per hour, at least 30mg of oxycodone daily, at least 8mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer. The optimal dose of Abstral® is determined by upward titration on an individual patient basis. The starting dose is 100mcg, titrating upwards until adequate analgesia with tolerable adverse reactions is achieved
Cost[2] – UK	The cost of a pack of 10 tablets (all strengths) is £49.99 = £5.00 per dose The cost of a pack of 30 tablets (all strengths) is £149.70 = £4.99 per dose

Background to breakthrough cancer pain

2

Definition

Breakthrough cancer pain (BTcP) has been defined as:

"A transient exacerbation of pain that occurs in otherwise stable background pain." [3]

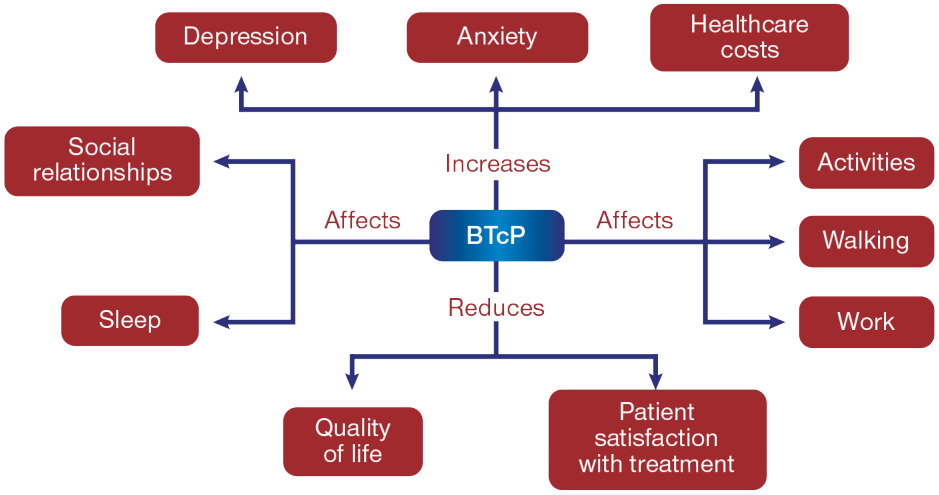
Studies have shown that it is variable in nature[4], and is experienced by 89% of hospice and 33% of community-based opioid-tolerant cancer patients.[5,6] Two sub-types are usually described:

- Incident/predictable[7]
  - Voluntary – movement such as walking
  - Involuntary – reflex movement such as coughing
  - Procedural –therapeutic intervention such as wound dressing
- Spontaneous/unpredictable[7]
  - Unrelated to an identifiable action

Impact of breakthrough cancer pain

The literature currently lacks a detailed specific analysis of the health-economic impact of BTcP, however several papers report associated significant negative impacts, including physical, psychological and economic impacts (see figure 1).[8,9]

Effects of breakthrough cancer pain on patients



Adapted from Zeppetella G. *European Oncology* 2009; **5**(1):10-13 DOI:[4]
(Sources: Portenoy et al 1999[8] and Caraceni et al 2004.[9])

Figure 1.

Evidence exists to suggest that unnecessary in-patient admissions can be minimised by improvement in pain management practices.[10]

Management of breakthrough cancer pain

A consensus panel has made recommendations on the management of BTcP.[11] The panel noted that the primary goal of pharmacological treatment of BTcP is to first make sure that the underlying baseline persistent pain is effectively treated. Once stable control of baseline pain has been established, the management goal is to decrease the frequency and intensity of BTcP.

The ideal treatment for BTcP is one which matches the characteristics of the pain episode, so should have a rapid onset of action[11] and a short duration of action. The development of transmucosal fentanyls has offered physicians a powerful pain killer which is absorbed quickly and has a relatively short half-life. The pharmacokinetics of transmucosal fentanyls are therefore appropriate for the treatment of individual episodes of BTcP.

Abstral® has been developed as a sublingually administered tablet to take advantage of the high absorbency offered by this route.

Clinical evidence 3

The pharmacokinetics, efficacy and tolerability profiles of Abstral® have been characterised through an extensive programme of studies.

3.1 Pharmacokinetic (PK) profile of Abstral®

The PK profile of Abstral® has been characterised through a series of eight Phase I studies. PK parameters were evaluated in healthy volunteers and opioid-tolerant cancer patients, with the study population encompassing multiple ethnicities and both genders.

Key findings

- Fentanyl was first quantifiable in plasma (T_{first}) at 8.0–10.7 minutes post-dose in opioid-tolerant patients with cancer, indicating that fentanyl is rapidly absorbed from the oral mucosa.[12] Rapid absorption across the oral mucosa indicates a PK profile that is appropriate for the treatment of BTcP
- The time to maximum fentanyl plasma concentration (T_{max}) was approximately 1 hour (range 22.5–240 minutes) in both opioid-tolerant patients with cancer, and healthy volunteers.[13-15] This indicates that the drug is rapidly absorbed into the systemic circulation, lending further support to the PK profile of Abstral® being well-suited for treating BTcP
- A single peak in plasma fentanyl concentration was observed following administration of Abstral®, suggesting that the majority of the dose was absorbed directly through the oral mucosa.[13-16] Absorption through the mucosa is desirable, as absorption in the gastrointestinal tract is slower and associated with lower bioavailability due to first-pass metabolism.[17] The bioavailability of Abstral® is calculated to be 54%[1]
- PK profiles were similar, following single and multiple dosing in healthy individuals, across the assessed dose range (100–800mcg). These results indicate that the PK parameters are independent of dose, and that the absorption of fentanyl through the oral mucosa is not reduced following higher or multiple doses.[12] Furthermore, accumulation of fentanyl following multiple dosing was limited,[13] therefore, Abstral® is suitable for treating patients with repeated episodes of BTcP. It is recommended that Abstral® should be used to treat no more than four BTcP episodes per day, and that patients should wait at least 2 hours before treating another episode of breakthrough cancer pain with Abstral®
- Dose proportionality was observed for all PK parameters assessed. The PK variables increased in a linear manner with ascending dose over the full range evaluated (100–800mcg), in both healthy patients and opioid-tolerant cancer patients.[11-13] Importantly, dose proportionality was observed following both single and multiple doses, indicating that patients should be able to reliably titrate Abstral® within the recommended dose range, to meet their individual analgesic requirements[13]
- PK profiles were independent of gender and ethnicity. The observed PK parameters showed no significant differences between men and women, or between Caucasian and Japanese participants[13,14]

Abstral® has a pharmacokinetic profile appropriate for the treatment of BTcP[17]

Abstral® SUBLINGUAL FENTANYL TABLET

3.2 Efficacy of Abstral®– Phase II and III studies

3.2.1 Efficacy of Abstral® for breakthrough cancer pain in opioid-tolerant patients[18]

Objectives

To establish the pharmacodynamic profile of Abstral®, and determine whether a dose range of 100–400mcg Abstral® provides effective and well-tolerated analgesia, and clinically therapeutic relief from BTcP, in adult opioid-tolerant cancer patients.

Methods

- A Phase II, Sweden-based, randomised, multi-centre, double-blind, crossover study consisting of four treatment periods
- Conducted in adult male and female patients with locally advanced or generalised cancer who were using opioid therapy for chronic cancer pain
- All patients were regularly experiencing at least four episodes of acute BTcP per day over a period of 14 days
- Patients received single doses of Abstral® 100mcg, 200mcg, 400mcg and placebo, in random order, at four pain episodes, each separated by a washout period of ≥1 day
- The efficacy variables assessed included pain intensity difference (PID – see appendix 1 for definition), global assessment of treatment and the need for rescue medication
- Patients were monitored for adverse events (AEs) throughout the study

Results

- A number of patients withdrew from the study before receiving study medication and 14 additional patients were recruited as replacement patients
- Of the total 38 recruited patients, 23 completed all four treatment periods according to protocol and 15 did not complete the study according to protocol
- Of the 15 patients that withdrew, 4 received partial treatment and were therefore included in the safety analysis
- Withdrawal from the study occurred for a number of reasons: protocol violations, insufficient number of pain episodes, withdrawal at patient's request, deterioration of medical status, serious AEs, or death
- Efficacy analyses were conducted in both the intent-to-treat population (ITT; n=27) and the per--protocol set (PPS; n=23)

- In the PPS, overall PID was significantly in favour of Abstral® 400mcg versus placebo (8.57mm, p<0.0001)
- Improvement in PID with Abstral® 400mcg showed statistical significance at 15 minutes compared with placebo (p=0.005; Figure 2)

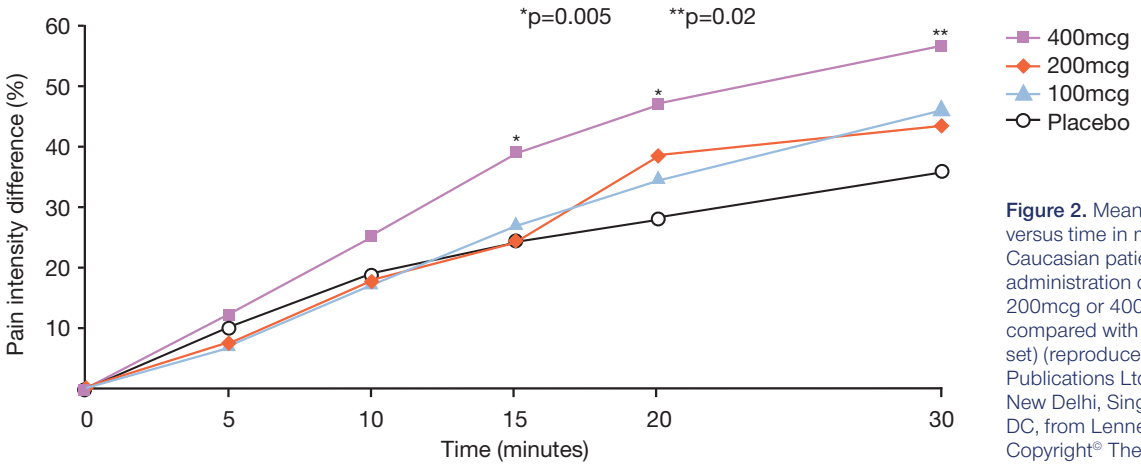


Figure 2. Mean pain intensity difference versus time in male and female Caucasian patients with cancer following administration of one single 100mcg, 200mcg or 400mcg dose of Abstral® compared with placebo (per–protocol set) (reproduced by permission of SAGE Publications Ltd., London, Los Angeles, New Delhi, Singapore and Washington DC, from Lennernas et al, 2010. Copyright© The Authors 2010).

- Improvements in PID in the PPS were reflected in the ITT population analysis (p=0.007 versus placebo; data not shown)
- There was a trend towards improved PID with Abstral® 100mcg and 200mcg in both the PPS and ITT population; however, this did not reach statistical significance versus placebo
- Twenty-two patients (95%) identified at least one dose of Abstral® that produced a clinically important decrease in pain intensity (PID ≥20mm)
- More patients treated with placebo required rescue medication compared to those treated with Abstral® 400mcg (15 vs. 5 respectively; p<0.001)
- Abstral® 400mcg provided significantly greater improvement in patient-assessed global treatment than placebo (9 patients rated treatment as “excellent” versus 3 for placebo; p=0.0146)
- A total of 15 AEs were reported by 13 patients during the study, of which pain and vomiting were the most frequent. Of the 15 AEs, two were considered to be probably or possibly related to the study drug
- No significant differences in the types and severity of AEs were observed with increasing dose

Conclusions

Abstral® 400mcg showed statistical superiority to placebo in the treatment of BTcP in opioid-tolerant adult cancer patients, with statistically significant improvements in pain being observed from 15 minutes after administration.

Abstral® was well-tolerated.

3.2.2 Efficacy and long-term tolerability of Abstral® for breakthrough cancer pain in opioid-tolerant patients[17]

Objectives

To assess the efficacy (in terms of improvements in pain intensity) and long-term safety of Abstral® for the treatment of BTcP in adult patients using opioid therapy for chronic cancer pain.

Methods

- Phase III, US-based, multi-centre, multiple-dose study comprising an open-label titration phase, a double-blind efficacy phase and an open-label long-term safety phase
- Conducted in adult male and female patients who were using opioid therapy for chronic cancer pain and regularly experiencing at least one, but not more than four, episodes of BTcP per day. Following a 2-week open-label titration phase to determine the effective dose of Abstral®, patients completed a 2-week, double-blind, placebo-controlled efficacy phase in which they received 10 treatment doses (7 Abstral® plus 3 matching placebo) in random order
- Patients rated pain intensity immediately before treatment and at 10,15, 30 and 60 minutes afterwards, using an 11-point scale (where 0 was “no pain” and 10 was “pain as bad as you can imagine”)
- PID was calculated by comparing pain intensity scores before and after treatment
- The primary endpoint was the summed pain intensity difference (SPID – see appendix 1 for definition) calculated from the plot of PID over time; from baseline to 30 minutes post-treatment
- Secondary endpoints included the SPID at 60 minutes post-treatment and the PID at 10,15, 30 and 60 minutes
- The efficacy phase was followed by a non-randomised, open-label safety phase of up to 12 months
- Rescue medication was permitted and patients were monitored for AEs throughout the study. Efficacy analysis was performed during the pre-specified interim analysis, and the safety analysis was conducted at the end of the study (performed on 75% of the total planned enrolment)

Results

Efficacy analysis

- The study enrolled 131 patients
- In total, 78 patients (59.5%) successfully identified a stable, effective dose of Abstral® during the titration phase
- Of these patients, 66 entered the efficacy phase and 60 then entered the long-term safety phase; a further 12 patients entered the long-term safety phase directly after titration
- The primary efficacy analysis was performed in 61 patients (ITT population)
- The mean SPID at 30 minutes following treatment administration was significantly greater with Abstral® than with placebo in the ITT set (49.5 and 36.6 for Abstral® and placebo, respectively, p=0.0004; Figure 3)
- Similarly, at 60 minutes, the mean SPID was significantly greater with Abstral® compared with placebo (p=0.0002; Figure 3)
- Abstral® gave rise to significantly improved PID relative to placebo from 10 minutes post-dose, (p=0.0055; Figure 4)
- Significant improvement in PID compared to placebo was maintained for 60 minutes (Figure 4)
- A greater proportion of patients displayed a response to therapy (defined as a pain intensity reduction of ≥30%) with Abstral® than with placebo (86.9% vs. 64.9%, respectively)

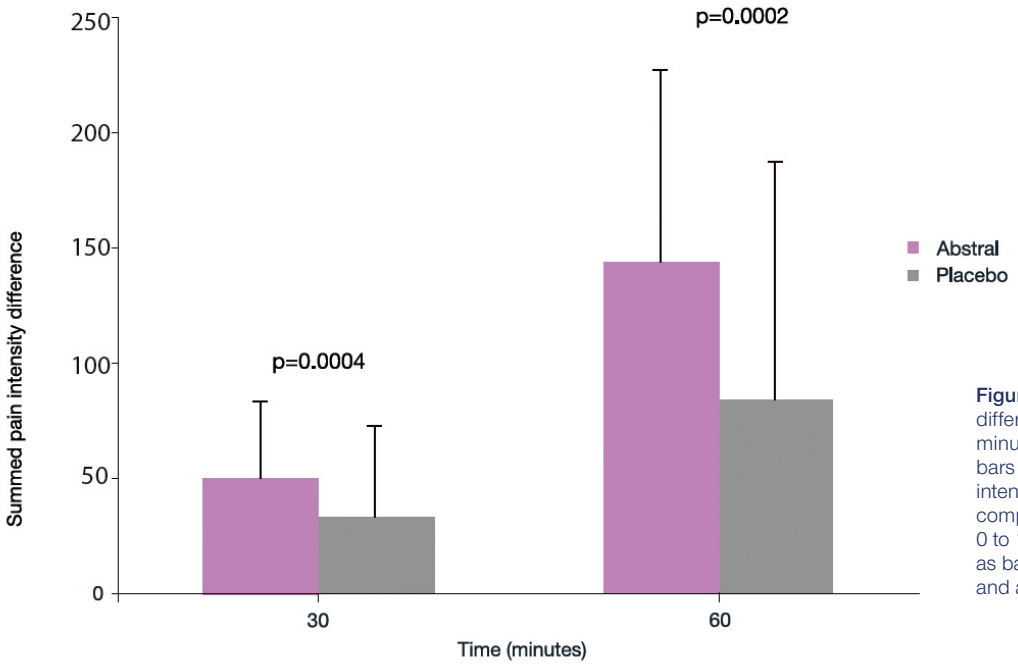


Figure 3. Mean summed pain intensity difference from baseline at 30 and 60 minutes with Abstral® and placebo. Error bars represent standard deviation. Pain intensity differences were calculated by comparing pain intensity scores (rated from 0 to 10, where 0 is "no pain" and 10 is "pain as bad as you can imagine") at baseline and after treatment (Rauck et al, 2009).

Abstral® gave rise to significantly improved PID relative to placebo from 10 minutes post-dose

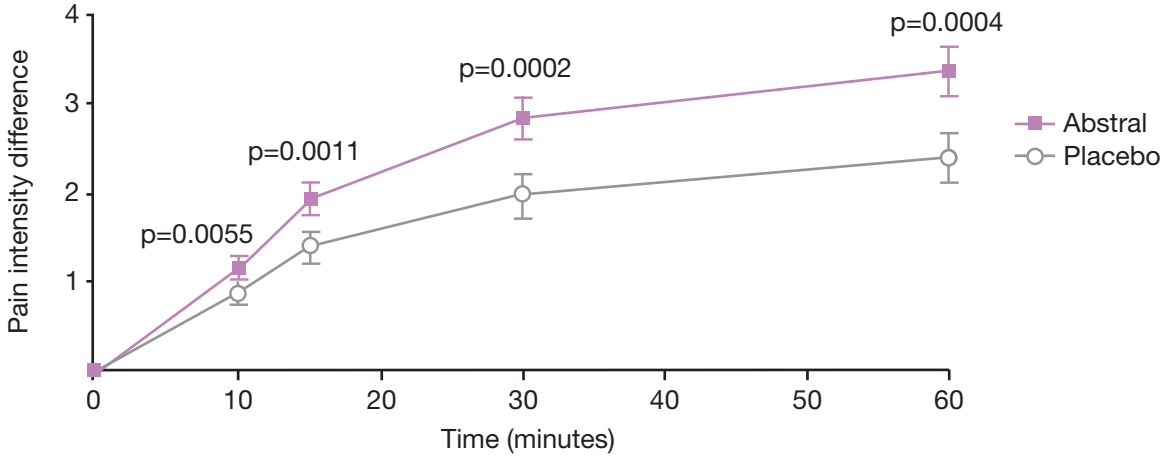


Figure 4. Mean pain intensity difference from baseline with Abstral® and placebo. Pain intensity difference was calculated by comparing pain intensity scores (rated from 0 to 10, where 0 is "no pain" and 10 is "pain as bad as you can imagine") at baseline and after treatment (Rauck et al, 2009).

Safety analysis

The safety analysis was conducted in a total of 131 patients, of whom 52 were treated for ≥3 months and 25 were treated for ≥12 months

- In total, 38,015 episodes of BTcP were treated with Abstral® during the long-term safety phase[11]
- The median dose during this phase was 600mcg (range 100–800mcg)
- Forty-one patients experienced at least one AE considered to be related to Abstral®
- The most common AEs related to Abstral® were nausea (12.2%), vomiting (5.3%), and somnolence (4.6%)
- Twenty-four patients experienced serious AEs (SAEs) during the study, of which one was considered to be study drug related (mild affect lability)
- Overall, the pattern of AEs was reflective of the underlying disease states of the patients and the long duration of the trial

Conclusions

Abstral® provided a statistically significant reduction in pain intensity compared to placebo from as early as 10 minutes after administration, and throughout the 60 minute assessment period

Furthermore, Abstral® was well-tolerated, with a safety profile comparable to other fentanyl formulations

3.2.3 Long-term effectiveness and tolerability of Abstral® for breakthrough cancer pain in opioid-tolerant patients[19]

Objectives

To assess the long-term effectiveness and safety of Abstral® for the treatment of BTcP in opioid-tolerant patients.

Methods

- A Phase III, US-based, multi-centre, multiple-dose study comprising a titration phase and a long-term maintenance phase
- The study was conducted in adult male and female patients who were using opioid therapy for chronic cancer pain and regularly experiencing at least one but not more than four episodes of BTcP per day
- Following a 2-week open-label titration phase to determine the effective Abstral® dose, patients entered a non-randomised, open-label safety phase of up to 12 months
- Rescue medication was permitted and patients were monitored for AEs throughout the study
- Effectiveness was evaluated using the patient's global evaluation of medication (PGEM), the brief pain inventory (BPI), and the depression, anxiety and positive outlook scale (DAPOS) – see appendix 1 for definitions

Results

The study enrolled 139 patients. Of these, 96 patients (69.1%) successfully identified a stable effective dose during the titration phase.

Effectiveness analysis

- Analysis of the PGEM data indicated that treatment with Abstral® was associated with significantly higher patient satisfaction with medication at the 6 month and end-of-study visits, compared to patients' pre-study pain medication, measured at screening ($p \leq 0.01$)
- BPI scores showed significant improvements in pain relief at 6 months and end-of-study, compared to screening ($p<0.05$)
- The composite score for interference of pain with daily activities was improved at both the 6 month and end-of-study visits, with statistically significant reductions being recorded at 6 months ($p<0.001$)
- DAPOS scores showed numerical trends towards improvement in all 3 quality of life (QoL) domains at end-of-study, compared to screening (Figure 5), with a statistically significant improvement in depression scores at 6 months ($p=0.011$)

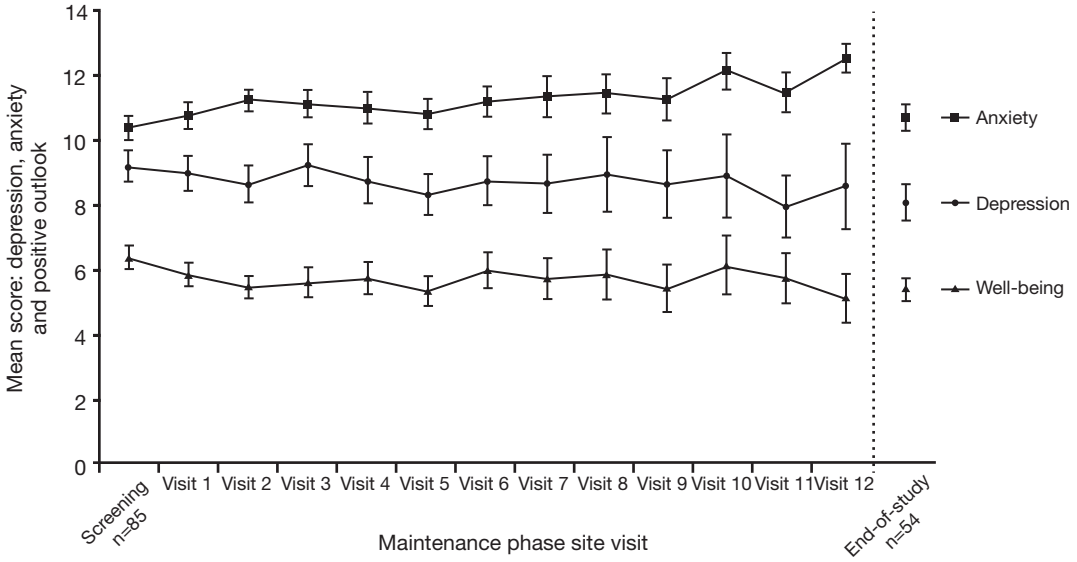


Figure 5. Mean scores for the three domains of the depression, anxiety and positive outlook scale (DAPOS), recorded at screening and throughout the long-term maintenance phase. Error bars represent standard error (Nalamachu et al, 2011)

Safety analysis

- The safety analysis included 139 patients, of whom 62 were treated for more than 3 months and 19 completed the full 12 months maintenance treatment
- The median stable dose was 400mcg (range 100–800mcg)
- A total of 46,952 episodes of BTcP were treated with Abstral® in the long-term maintenance phase
- In total, 49 patients experienced at least one AE that was considered to be probably or possibly related to the study drug. The most common Abstral®-related AEs were nausea (8.6% of patients), constipation (5.8%) and somnolence (5.8%)
- SAEs were reported by 46 patients (33.1%). The profile of SAEs was reflective of the underlying disease states and physical conditions of the patients. None of the SAEs were considered to be related to Abstral®

Conclusions

The findings of this study demonstrate that Abstral® is an effective and well-tolerated treatment for BTcP, with a safety profile similar to that of other currently available fentanyl products.

3.3 Efficacy of Abstral® in clinical practice – Phase IV study

3.3.1 Abstral® in daily clinical practice: efficacy, safety and tolerability in patients with breakthrough cancer pain[20]

Objectives

To evaluate the efficacy, QoL impact and safety of Abstral® for the treatment of BTcP in cancer patients in routine clinical practice.

Methods

- A prospective, open-label Phase IV study conducted at 47 treatment centres in Germany
- Opioid-tolerant male and female adult cancer patients with BTcP who had been prescribed Abstral® for the first time were eligible for enrolment
- All patients were using opioid therapy for chronic cancer pain prior to study commencement, and Abstral® was titrated as necessary to find an effective and tolerable dose
- Patients self-administered Abstral® on an as-needed basis for BTcP episodes, and completed questionnaires related to their health and treatment over a 28-day observation period
- Efficacy was assessed using the patient-reported times to first effect and maximum effect of Abstral®, and measures of maximum BTcP intensity (Appendix 2)
- Patients who had previously used alternative supplementary pain relief medication for BTcP also scored the effectiveness of Abstral® compared to their previous medication
- Changes in QoL were evaluated using the modified pain disability index (mPDI) and the hospital anxiety and depression scale (HADS; Appendix 2)
- AEs were recorded throughout the 28-day observation period both by patients and by clinicians. Subgroup analyses were performed to examine the efficacy of Abstral® in patients who previously reported limited response to oral transmucosal fentanyl citrate ('OTFC non-responders') and immediate-release morphine ('IRM non-responders')[21,22]

Results

Efficacy and QoL

- The study enrolled 217 patients; of these, 181 (83.4%) completed the 28-day observation period
- There was a significant improvement in pain intensity recorded for BTcP episodes treated with Abstral®, compared with baseline (2.6 vs 7.8; $p<0.0001$; Figure 6)

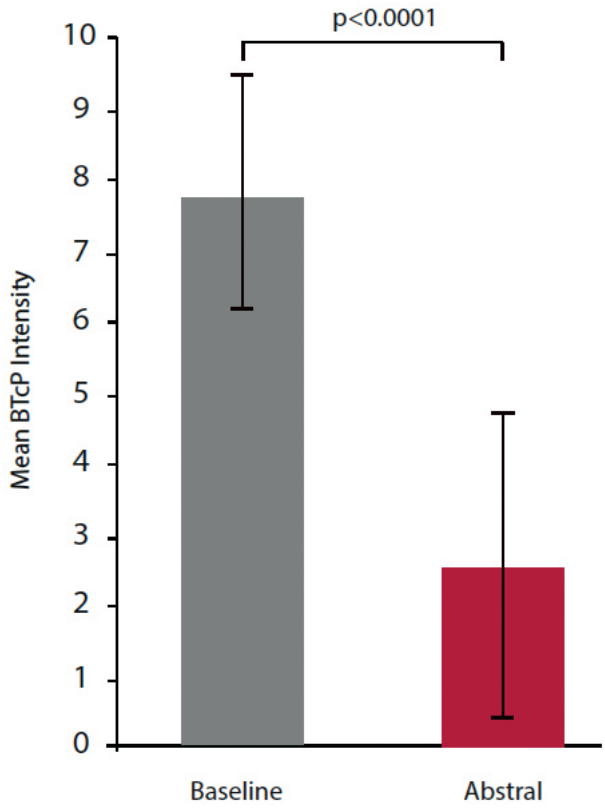


Figure 6. Mean scores for maximum intensity of BTcP at the time of enrolment (baseline) and after administration of Abstral®. Error bars represent standard deviation (Überall MA, Müller-Schwefe GHH, 2011).

- Patients reported experiencing the first effects of Abstral® by 10 minutes after administration in 82.8% of episodes, and a time to maximum effect of ≤30 minutes in 63.2% of episodes (Figure 7)
- Interestingly, OTFC non-responders (n=7) and IRM non-responders (n=35) also recorded an onset of action by 10 minutes and maximum effect within 30 minutes of administration in the majority of episodes (Figure 7)[21,22]

Patients reported experiencing the first effects of Abstral® by 10 minutes after administration in 82.8% of BTcP episodes.

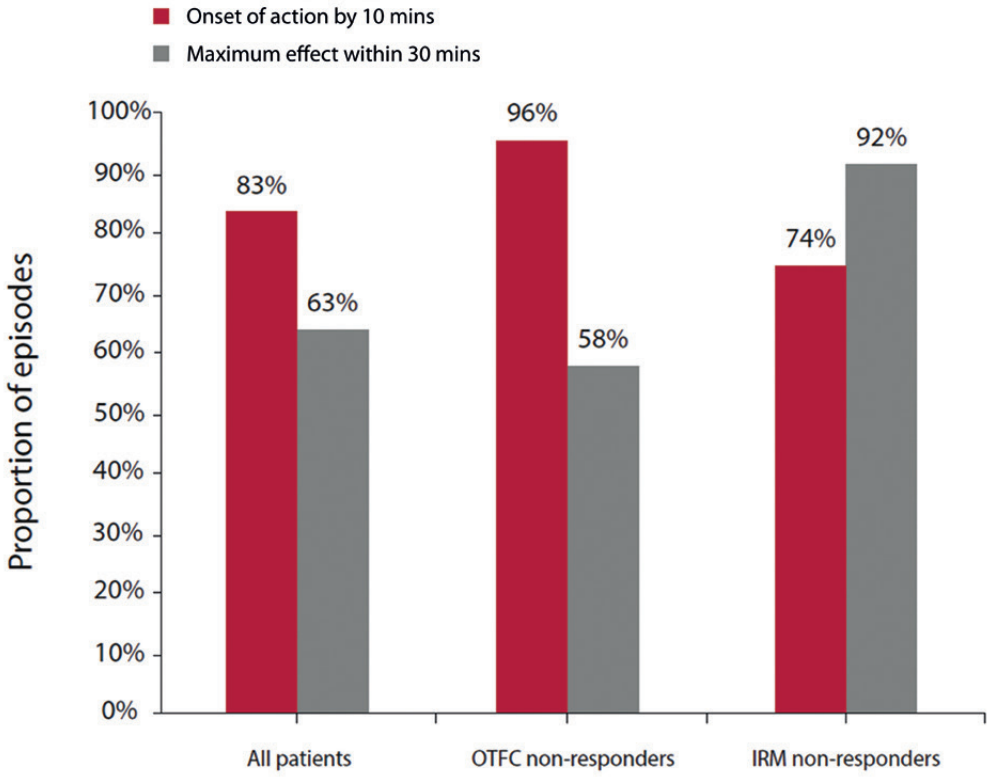


Figure 7. Time to onset of action and time to maximum effect following administration of Abstral® (Überall MA, Müller-Schwefe GHH, 2011).

- In all, 83 patients had previously used a different medication for BTcP
  - Among 53 patients who recorded full details of their previous medication, the most common included IRM (66.0%), OTFC (13.2%) and immediate-release hydromorphone (9.4%)
  - The majority of the 83 patients with previous experience reported that, compared to previous medication, Abstral® was better in terms of speed of action (87.7% of patients), strength of action (85.7%), duration of action (83.9%), tolerability (88.6%) and ease of handling (87.3%)
  - QoL scores indicated that treatment with Abstral® gave rise to significant improvements in both physical and emotional functioning during the observation period.[13] The proportion of patients experiencing high levels of pain-related disability, anxiety and depression were significantly reduced at end-of-study compared with enrolment ($p<0.0001$; Table 1)
  - QoL scores were also significantly improved from baseline in OTFC non-responders and IRM non-responders[21,22]

Table 1. Proportion of patients experiencing impaired QoL (Überall MA, Müller-Schwefe GHH, 2011)

	Enrolment n=217 % of patients	End of study n=181 % of patients	p-value
High pain-related disability*	73.0	12.1	<0.0001
Abnormal levels of anxiety†	54.5	1.6	<0.0001
Abnormal levels of depression†	70.3	15.6	<0.0001

*Defined as a score >40 on the modified pain disability index; †defined as a score >11 on the relevant subscale of the hospital anxiety and depression scale.

Dose titration

- The median dose of Abstral® was 400mcg per episode
- Titration of Abstral® provided improvements in pain intensity over the first four BTcP episodes treated, and over the 28-day treatment period[22]

Safety

- All 217 enrolled patients received at least one dose of Abstral®, and a total of 3163 BTcP episodes were treated during the study
- A total of 12 patients (5.5%) experienced at least one study drug-related AE, the most common of which included nausea (2.8%), somnolence (2.3%), dizziness (0.9%), and vomiting (0.9%)
- Of the 21 deaths that occurred during the study, none were considered to be Abstral®-related

Conclusions

Abstral® represents an effective, well-tolerated treatment option that can potentially enhance QoL in opioid-tolerant cancer patients treated for BTcP. Study treatment was associated with significant improvements in BTcP intensity and QoL scores, and patients reported rapid onset of action in the majority of episodes.

Abstral®– patient acceptability

3.3.2 How practical are transmucosal fentanyl products for breakthrough cancer pain? Novel use of placebo formulations to survey user opinion[23]

Objectives

Survey opinion amongst cancer patients on practical aspects of the use of Abstral® placebo sublingual tablets, placebo buccal/sublingual tablets and placebo nasal spray, to help inform recommendation on local formulary adoption.

Methods

- A survey assessing the opinions of patients attending day care at a specialist palliative care centre, results anonymised
- Inclusion criteria – use of strong opioids for background and breakthrough episodes of cancer pain
- Each participant was given a placebo of each product and asked to access it (through the packaging which was identical to active equivalent), and administer it having been given standardised verbal and written instructions as per the product literature
- Assessments were also made for the users usual rescue medication for comparison
- Time taken for complete dissolution for Abstral® placebo and placebo buccal/sublingual tablets was recorded by stop watch
- Assessments were made on ease of administration, palatability, ease of access of packaging and overall impression. Responses recorded on a 1-7 Likert agree-disagree scale (1= extremely positive, 4= neutral, 7= extremely negative)
- Participants were asked if they would be prepared to use each product and which was their most preferred product

Results

- 30 patients completed the survey; mean age 65 +/-8; equal male/female split
- Abstral® placebo received a median score of 1 for ease of administration (‘definitely easy’); placebo buccal/sublingual tablets and placebo nasal spray scored a median of 2 (‘moderately easy’) (p=0.04 and 0.05 respectively)
- Dissolution time recorded for Abstral® placebo–57 seconds (range 37 secs–72 secs), time for placebo buccal/sublingual tablets–323 seconds (range 186–443 secs). (Figure 8)
- 20 positive comments were reported relating to the convenience of Abstral® placebo, 18 negative comments for placebo buccal/sublingual tablets. The number of negative comments relating to the convenience of Abstral placebo and the number of positive comments for placebo buccal/sublingual tablets was not reported

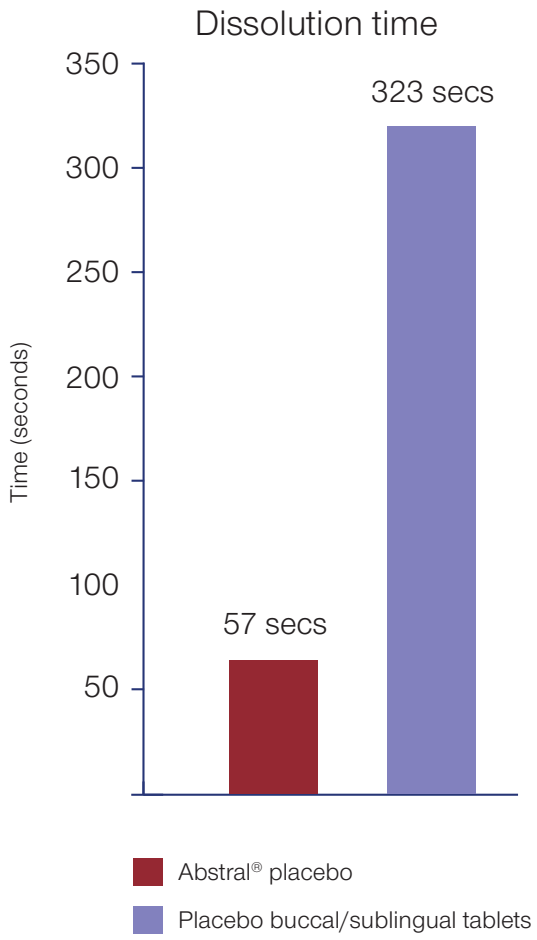


Figure 8. Median time to complete dissolution for Abstral® placebo and placebo buccal/sublingual tablets (England R et al).

- Abstral® placebo scored a median of 2 for palatability ('moderately like'); placebo buccal/sublingual tablets and placebo nasal spray scored 4 ('neutral') ($p<0.01$ vs placebo buccal/sublingual tablets)
- 12 positive comments were reported related to taste and speed of dissolution for Abstral® placebo; mixed comments for placebo buccal/sublingual tablets for taste and effervescence
- 90% (27) of patients indicated they would be prepared to use Abstral® placebo, compared to 60% (18) and 57% (17) for placebo buccal/sublingual tablets and placebo nasal spray respectively (figure 9)
- 60% (18) rated Abstral® placebo as their most preferred product compared to 20% (6) and 7% (2) for placebo buccal/sublingual tablets and placebo nasal spray respectively (figure10)
- Free-text comments indicated Abstral® placebo popular because of the relative ease of access (packaging), lack of taste and speed of dissolution

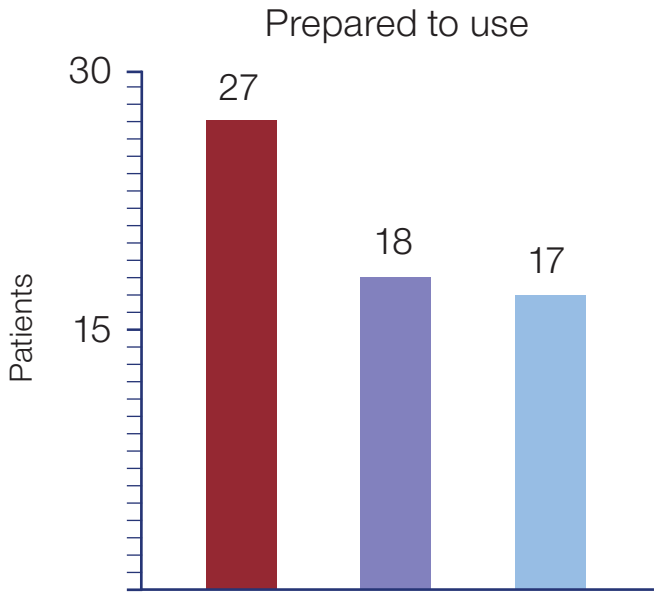


Figure 9. Prepared to use (England R et al. 2011).

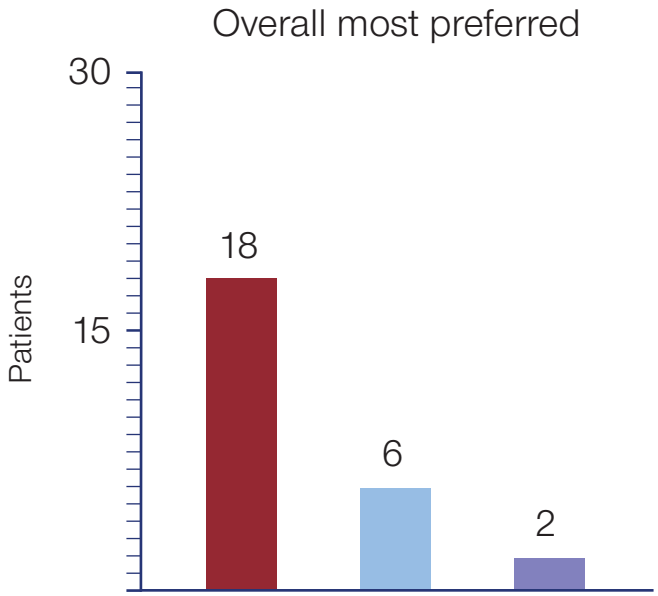


Figure 10. Overall most preferred product (England R et al. 2011)

Abstral® placebo

Placebo buccal/sublingual tablets

Placebo nasal spray

Conclusion

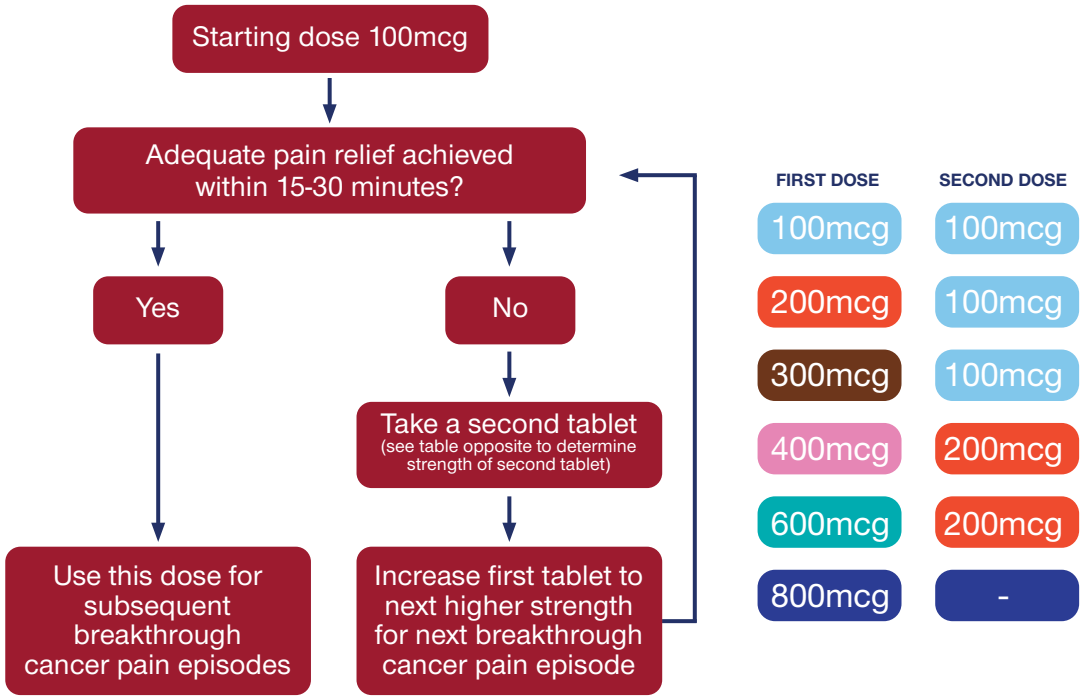
Relative to the placebo buccal/sublingual tablets and placebo nasal spray, the Abstral® placebo was generally easier to access, administer and more palatable. Consequently more participants indicated that they would be prepared to use this product and rated it as their most preferred product.

Titration

The optimal dose of Abstral® must be determined by upward titration on an individual patient basis. Several doses are available for use during the dose titration phase. An initial dose of Abstral® 100mcg should be used, titrating upwards as necessary through the range of available dosage strengths as shown in the diagram below:

Guidelines for prescribing Abstral®

- Switching from other fentanyl containing products to Abstral® must not occur at a 1:1 ratio because of different absorption profiles. If patients are switched from another fentanyl-containing product, a new dose titration with Abstral® is required
- Starting dose is 100 micrograms
- Maximum dose is 800 micrograms
- During titration, patients can be instructed to use multiples of 100 microgram tablets and/or 200 microgram tablets for any single dose
- The total dose for a single episode of BTcP during the titration phase includes the first tablet(s) taken plus the supplemental tablet(s), if required
- DO NOT USE more than 2 doses of Abstral® per episode of BTcP
- No more than four (4) tablets should be used at any one time
- No more than 4 episodes of BTcP should be treated in any 24 hour period
- Patients should wait at least 2 hours before treating another episode of BTcP with Abstral®
- If adequate analgesia is achieved at the higher dose, but undesirable effects are considered unacceptable, an intermediate dose (using the 100 microgram tablet where appropriate) may be administered
- In order to minimise the risk of opioid–related adverse reactions and to identify the appropriate dose, it is imperative that patients be monitored closely by health professionals during the titration proces
- Consult the Summary of Product Characteristics for more information



Patients should be carefully monitored until an optimal dose is achieved.

Prescribers of transmucosal fentanyl products should understand that different formulations are not bio-equivalent and thus not interchangeable; when switching products, individual titration from the lowest available dose is required.[24]

Abstral® SUBLINGUAL FENTANYL TABLET

Further information

If you require further medical information on Abstral®, please contact Kyowa Kirin International UK NewCo Ltd (known as “Grünenthal Meds”):

By phone: 01896 664000

By email: medinfo@kyowakirin.com

Appendix 1

Brief pain inventory (BPI)	The BPI comprised six questions relating to pain and physical functioning. Patients rated their worst, least and average pain in the last 24 hours, and pain at the time of assessment, using a numerical scale from 0 ('no pain') to 10 ('pain as bad as you can imagine'). Patients also rated pain relief in 10% increments from 0% ('no relief') to 100% ('complete relief'). Another numerical scale, from 0 ('does not interfere') to 10 ('completely interferes'), was used to rate interference of pain with seven aspects of daily functioning: general activity, mood, walking ability, normal work, relationships, sleep and life enjoyment.
Depression, anxiety and positive outlook scale (DAPOS)	Changes in psychological factors associated with pain were recorded using the DAPOS, comprising 11 statements among three QoL domains (depression, anxiety and well-being). Patients indicated their agreement with the statements on a 5-point scale ranging from 1 ('almost never') to 5 ('almost all the time'). Higher scores correspond to greater depression, greater anxiety, and greater well-being, respectively.
Pain intensity difference (PID)	A measure of the difference in pain intensity from immediately before treatment (at baseline) to after treatment. Indicates the analgesic efficacy of the drug. Pain intensity score assessed on an 11 point scale, where 0 is "no pain" and 10 is "pain as bad as you can imagine" at each acute pain episode, immediately before treatment and at 10, 15, 30 and 60 minutes afterwards. PID calculated by subtracting the pain intensity score at each time point from the pain intensity score at baseline.
Patients' global evaluation of medication (PGEM)	In the PGEM assessment, patients rated their satisfaction with their pain medication (very satisfied, satisfied, no preference, dissatisfied or very dissatisfied) by responding to the following question: 'How satisfied are you overall with your current medication for pain?'.
Summed pain intensity difference (SPID)	A measure of the overall performance of the study drug, over 30 or 60 minutes. Indicates the analgesic efficacy of the drug. Calculated based on a plot of PID against time.

Appendix 2

Efficacy parameters assessed in the Überall MA and Schwelbe-Müller GHH, 2011 post-marketing surveillance study

Efficacy variable	Reason for assessment
Pain intensity	Patients rated the maximum pain intensity experienced during BTcP episodes • On an 11 point scale from 0 = no pain, to 11 = strongest pain imaginable • At enrolment (baseline) and after each dose of Abstral®
Timing of pain relief	Patients selected from a list of time intervals • In response to two prompts: "Time to first effect" and "Time to maximum effect" • After each dose of Abstral®
Comparison with previous medication	Patients rated Abstral® in comparison with previous medication: In terms of speed, strength, and duration of action; tolerability; ease of handling ON a 7 point scale, from "very much better" to "very much worse"
Modified pain disability index (mPDI)	Patients indicated their level of physical disability • In each of 7 dimensions of daily functioning • Using an 11-point scale from 0 = no disability, to 10 = complete disability • At enrolment and end of study
Hospital anxiety and depression scale (HADS)	Patients indicated their level of emotional functioning: • In response to 7 statements on the anxiety subscale and 7 on the depression subscale • By choosing from 4 responses Each response carried a score, allowing a total to be calculated for each subscale

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Prescribing information

Prescribing Information Abstral® (fentanyl (as citrate)) Sublingual Tablets

Please refer to the full Summary of Product Characteristics before prescribing.

Name: Abstral sublingual tablets. **Active Ingredient:** 100mcg, 200mcg, 300mcg, 400mcg, 600mcg or 800mcg fentanyl (as citrate). **Indication:** Management of breakthrough pain (BTP) in adult patients using opioid therapy for chronic cancer pain. **Dosage and administration:** Administer directly under the tongue, and allow to dissolve without chewing, sucking or swallowing the tablet. ***Adults;*** Initially 100mcg, titrating upwards as necessary with close monitoring to establish an appropriate dose. Patients should wait at least 2 hours before treating another episode of breakthrough pain and take no more than 4 doses/day. Abstral should be discontinued immediately if BTP episodes cease. Treatment for the persistent background pain should be kept as prescribed. If discontinuation of all opioid therapy is required, closely monitor to avoid the possibility of abrupt withdrawal effects. ***Elderly and patients with renal and hepatic impairment;*** Take particular care during titration and monitor for signs of fentanyl toxicity. ***Children and adolescents;*** Must not be used in patients under 18 years of age. **Adverse effects:** The most serious adverse effects include respiratory depression, hypotension and shock. The most frequent adverse reactions include nausea, constipation, somnolence, headache, dizziness, dyspnoea, stomatitis, vomiting, dry mouth, hyperhidrosis and fatigue. Other serious but uncommon adverse reactions include hypersensitivity, tachycardia, bradycardia, hypotension, depressed level of consciousness, loss of consciousness and drug withdrawal syndrome. Coma is also known to occur. Cheyne Stokes respiration has been observed in cases of fentanyl overdose. Prescribers should consult the summary of product characteristics for further details of side effects. **Precautions:** Abstral should be used with caution in patients with previous or pre-existing bradyarrythmias; care should be taken in treating patients with hypovolaemia and hypotension. Abstral must be kept out of sight and reach of children. Ensure patients and carers use correctly and know what to do in case of overdose. Before starting Abstral, ensure long-acting opioid treatment for persistent pain is stable. Dependence may develop upon repeated administration of opioids. Repeated use of Abstral may lead to Opioid Use Disorder (abuse and dependence) Take care during dose titration in patients with COPD or at risk of respiratory depression. Administer with extreme caution in patients susceptible to the intracranial effects of hyperkapnia. Opioids may mask the clinical course in patients with head injuries. Use with caution in patients with mouth wounds or mucositis. Monitor use carefully in elderly, cachectic and debilitated patients, and patients with liver or kidney dysfunction. A potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs. Discontinue Abstral if serotonin syndrome is suspected. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered. Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep related hypoxaemia. **Interactions:** Use with caution if given concomitantly with CYP3A4 inhibitors and/or inducers, other CNS depressants, alcohol or partial opioid agonists/antagonists. Co-administration of a serotoninergic agent, such as a Selective Serotonin Reuptake Inhibitor, a Serotonin Norepinephrine Reuptake Inhibitor or a Monoamine Oxidase Inhibitor, may increase the risk of serotonin syndrome. Concomitant use of other CNS depressants, such as other morphine derivatives (analgesics and antitussives), general anaesthetics, gabapentinoids (gabapentin and pregabalin), skeletal muscle relaxants, sedative antidepressants, sedative H1 antihistamines, barbiturates, anxiolytics (i.e., benzodiazepines), hypnotics, antipsychotics, clonidine, and related substances may produce increased CNS depressant effects, increased risk of sedation, respiratory depression, hypotension, coma and death because of additive CNS depressant effect. Not recommended for use in patients who have received an MAOI within 14 days **Pregnancy:** Fentanyl should only be used during pregnancy when clearly necessary. Do not use during labour and delivery. **Lactation:** Fentanyl should not be used by breastfeeding women. **Contraindications:** Hypersensitivity to any of the ingredients; opioid naïve patients; severe respiratory depression or severe obstructive lung conditions. Treatment of acute pain other than BTP. Patients being treated with medicinal products containing sodium oxybate **Further information available on request from the Marketing Authorisation Holder. Legal classification:** CD POM. **Date of prescribing information:** October 2022.

For the United Kingdom:

Marketing Authorisation Holder: Kyowa Kirin Ltd., Galabank Business Park, Galashiels, Scotland TD1 1QH, UK.

Pack Sizes & NHS cost: Abstral 100-400mcg 10 tablets: £49.99. Abstral 100-800mcg 30 tablets: £149.70. **Marketing Authorisation Numbers:** PL 16508/0030-35.

Adverse Events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk. Adverse Events should also be reported to Kyowa Kirin Ltd. on +44 (0)1896 664000, email medinfo@kyowakirin.com

For the Republic of Ireland:

Marketing Authorisation Holder: Kyowa Kirin Holdings B.V., Bloemlaan 2, 2132NP Hoofddorp, The Netherlands.

Pack Sizes: Abstral 100-400mcg 10 tablets. Abstral 100-800mcg 30 tablets. **Marketing Authorisation Numbers:** PA2288/004/002/002-007.

Adverse Events should be reported. Information about adverse event reporting can be found at www.hpra.ie. Adverse Events should also be reported to Kyowa Kirin Ltd. on +44 (0)1896 664000, email medinfo@kyowakirin.com