AUSTRALIAN PRODUCT INFORMATION – ABSTRAL® fentanyl (as citrate)

WARNINGS

Limitations of Use

Because of the risks associated with the use of opioids, ABSTRAL (fentanyl citrate sublingual tablets) should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hazardous and harmful use

ABSTRAL poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of ABSTRAL. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking ABSTRAL.

1. NAME OF THE MEDICINE

Fentanyl (as citrate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 100, 200, 300, 400, 600, or 800 micrograms of fentanyl (as citrate).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ABSTRAL fentanyl (as citrate) 100 micrograms sublingual tablets (round-shaped, white, flat-faced, bevel-edged tablet)

ABSTRAL fentanyl (as citrate) 200 micrograms sublingual tablets (oval-shaped, white, flat-faced, bevel-edged tablet)

ABSTRAL fentanyl (as citrate) 300 micrograms sublingual tablets (triangle-shaped, white, flat-faced, bevel-edged tablet)

ABSTRAL fentanyl (as citrate) 400 micrograms sublingual tablets (diamond-shaped, white, flat-faced, bevel-edged tablet)

ABSTRAL fentanyl (as citrate) 600 micrograms sublingual tablets ("D"-shaped, white, flat-faced, bevel-edged tablet)

ABSTRAL fentanyl (as citrate) 800 micrograms sublingual tablets (caplet-shaped, white, flat-faced, bevel-edged tablet)

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ABSTRAL is indicated for the management of breakthrough pain in adults with cancer who are already receiving maintenance opioid therapy for chronic pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

ABSTRAL should only be administered to patients who are considered tolerant to their opioid therapy for persistent cancer pain. Patients can be considered opioid tolerant if they take at least 60 mg of oral morphine daily or an equianalgesic dose of another opioid for a week or longer.

ABSTRAL sublingual tablets should be administered directly under the tongue at the deepest part. ABSTRAL sublingual tablets should not be swallowed, but allowed to completely dissolve in the sublingual cavity without chewing or sucking. Patients should be advised not to eat or drink anything until the sublingual tablet is completely dissolved.

In patients who have a dry mouth, water may be used to moisten the buccal mucosa **before** taking ABSTRAL.

Dose Initiation, Titration and Maintenance

ABSTRAL dose must be individually upwardly titrated until the optimal maintenance dose for ongoing treatment of breakthrough cancer pain episodes is achieved.

The objective of dose titration is to identify an optimal maintenance dose for ongoing treatment of breakthrough cancer pain episodes. This optimal dose should provide adequate analgesia with an acceptable level of adverse reactions. Rescue medication can be used if adequate analgesia is not achieved after use of ABSTRAL during the titration period.

The initial dose of ABSTRAL used should be 100 micrograms, titrating upwards as outlined below. Patients should be carefully monitored until an optimal dose is reached.

ABSTRAL is not a generic of any other fentanyl product. Due to differences in the pharmacokinetic properties of different fentanyl products and the individual variability of patients, patients switching from other fentanyl-containing products to ABSTRAL must also start with the initial 100 microgram dose. ABSTRAL is not equivalent on a microgram per microgram (1:1) basis with all other fentanyl products; therefore, do not switch patients on a microgram per microgram basis from any other fentanyl product (see Section: Titration in patients switching between immediate-release fentanyl-containing products).

The following steps are recommended for initiation and titration; although in all cases the physician should take into account the clinical need of the patient, age and concomitant illness.

Dose Initiation and Titration

No more than two (2) doses of ABSTRAL, taken 30 minutes apart, should be administered for a single episode of breakthrough cancer pain during the titration phase. Wait 2 hours before treating another episode of breakthrough cancer pain

Initiation

All patients must initiate therapy with a single 100 microgram sublingual tablet. If adequate analgesia is achieved within 30 minutes of administration of a single dose, no titration is required and this dose should be used as the maintenance dose for the next breakthrough cancer pain episodes.

If adequate analgesia is not obtained within 30 minutes of administration, a supplemental (second) 100 microgram sublingual tablet may be administered (refer to Diagram 1). As analgesia was inadequate from a single 100 microgram dose at initiation, upwards titration may be necessary (see *Titration* below). Allow for at least 2 hours before treating the next breakthrough cancer pain episode with ABSTRAL.

Titration

If analgesia was inadequate from a single 100 microgram dose at initiation, a 200 microgram dose should be administered for the next episode of breakthrough cancer pain (refer to Diagram 1).

Similar to the initiation stage, if adequate analgesia is achieved within 30 minutes with the newly titrated dose, no further titration is required and this dose should be used as the maintenance dose for future breakthrough cancer pain episodes.

If adequate analgesia is not obtained within 30 minutes of administration of the 200 microgram dose, a supplemental (second) 100 microgram sublingual tablet may be administered for that breakthrough cancer pain episode (refer to Diagram 1). As adequate analgesia was not obtained within 30 minutes of taking the newly titrated dose (200 micrograms), an increase in dose to the next highest tablet strength should be considered for the next episode of breakthrough cancer pain (refer to Diagram 1).

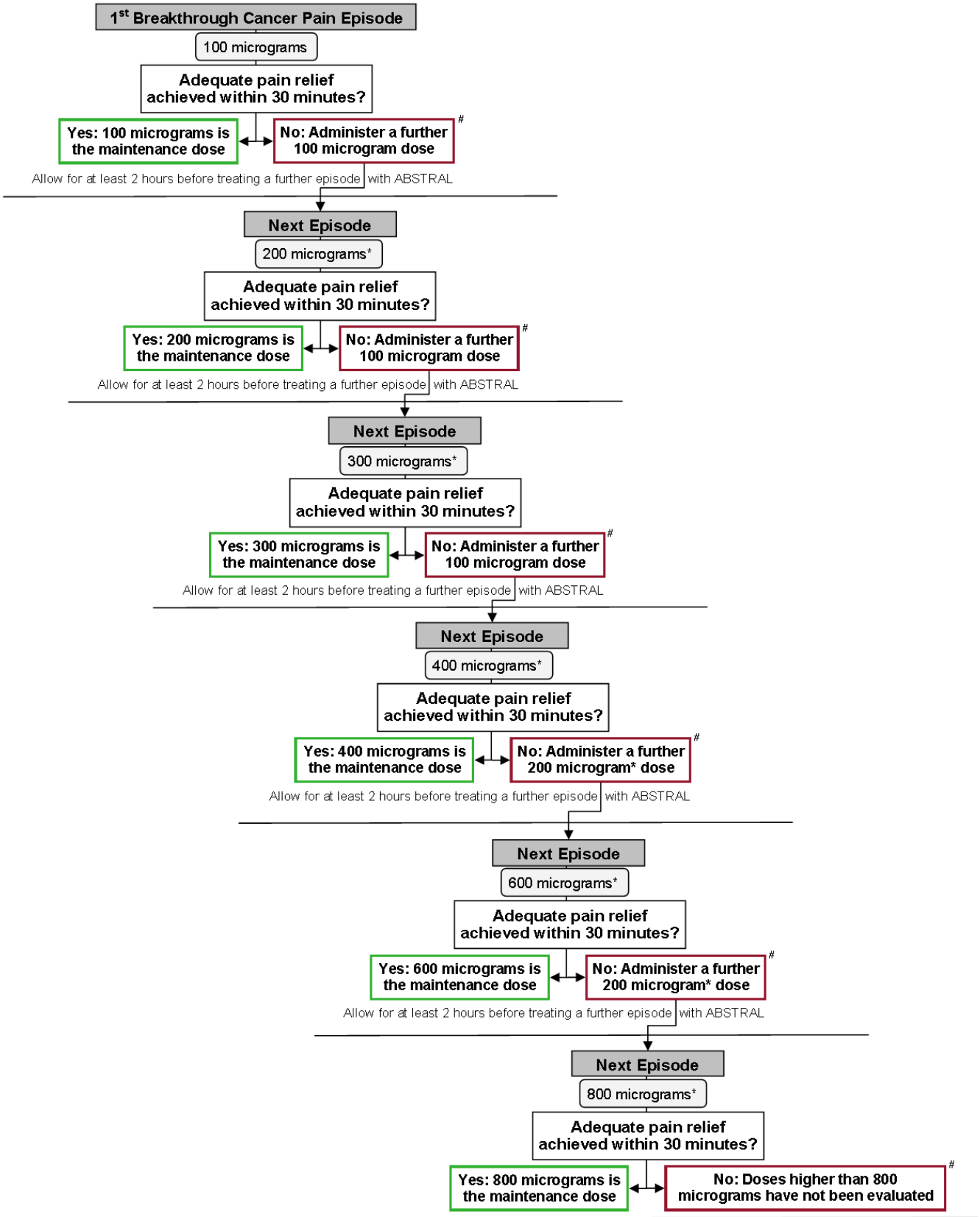
Dose escalation should continue in this stepwise manner for subsequent breakthrough cancer pain episodes until adequate analgesia with tolerable adverse reactions is achieved. For starting doses of 400 micrograms and higher the supplemental (second) sublingual tablet should be 200 micrograms (Refer to Diagram 1).

If adequate analgesia is achieved at the higher dose, but side effects are considered unacceptable, an intermediate dose (using the 100 microgram sublingual tablet where appropriate) may be administered for the next episode of breakthrough cancer pain.

The efficacy and safety of doses higher than 800 micrograms have not been evaluated in clinical studies; therefore, doses higher than 800 micrograms are not recommended.

During titration, patients can be instructed to use multiples of 100 microgram tablets and/or 200 microgram tablets for any single dose. No more than four (4) tablets should be used at any one time. 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 healthcare professionals during the titration process.

During titration patients should wait at least two (2) hours before treating another episode of breakthrough cancer pain with ABSTRAL.



* May use multiples of 100 microgram tablets and/or 200 microgram tablets but not more than four (4) tablets at any one time.

\# Rescue medication can be used if adequate analgesia is not achieved after use of ABSTRAL during the titration period

Diagram 1: ABSTRAL Titration Process

Maintenance therapy

Once an optimal dose has been established, which may be more than one tablet, patients should be maintained on this dose.

Patients should not take more than four (4) ABSTRAL doses per day.

During the maintenance period patients should wait at least two (2) hours before treating another episode of breakthrough cancer pain with ABSTRAL.

Dose re-adjustment

If the response (analgesia or adverse reactions) to the titrated ABSTRAL dose markedly changes, an adjustment of dose may be necessary to ensure that an optimal dose is maintained.

If more than four (4) episodes of breakthrough cancer pain are experienced per day over a period of more than four (4) consecutive days, re-evaluate the dose of the long-acting opioid used for background, cancer-related pain.

If the long-acting opioid or dose of long-acting opioid is changed, re-evaluate and re-titrate the ABSTRAL dose as necessary to ensure the patient is on an optimal dose.

It is imperative that any dose re-titration of any analgesic is monitored by a healthcare professional.

Discontinuation of ABSTRAL therapy

ABSTRAL should be discontinued immediately if the patient no longer experiences breakthrough cancer pain episodes. The treatment for the persistent background pain should be kept as prescribed.

If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor in order to avoid the possibility of abrupt withdrawal effects (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Ceasing Opioids).

Titration in patients switching between immediate-release fentanyl-containing products

Fatal respiratory depression has occurred in patients treated with immediate-release transmucosal fentanyl, including following use in opioid non-tolerant patients and improper dosing.

The substitution of any one fentanyl product for any other fentanyl product may result in fatal overdose unless the new product is titrated from the recommended starting dose. When prescribing, do not convert patients on a microgram-per-microgram (1:1) basis from any other fentanyl products to ABSTRAL.

Substantial differences may exist in the pharmacokinetic profile of immediate-release fentanyl products, which result in clinically important differences in the rate and extent of absorption of fentanyl. Therefore, when switching between fentanyl-containing products indicated for treatment of breakthrough cancer pain, including intranasal formulations, it is essential that patients are titrated with the new product, and not switched on a dose-for-dose (microgram-for-microgram) basis.

Use in children and adolescents

ABSTRAL must not be used in patients less than 18 years of age due to a lack of data on safety and efficacy.

Use in elderly patients

Dose titration needs to be approached with particular care and patients observed carefully for signs of fentanyl toxicity (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in patients with renal and hepatic impairment

Patients with kidney or liver dysfunction should be carefully observed for signs of fentanyl toxicity during the ABSTRAL titration phase (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Special precautions for disposal

Waste material should be disposed of safely. Patients/carers should be encouraged to return any unused product to the pharmacy, where it should be disposed of in accordance with national and local requirements.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Non opioid-tolerant patients because of the risk of life-threatening respiratory depression.
- Severe respiratory disease, severe obstructive lung conditions, acute respiratory disease and respiratory depression.
- Use in patients not receiving opioid maintenance therapy for cancer-related pain.
- Use in patients for non-breakthrough cancer pain,
- Use in patients for acute and chronic non-cancer pain.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Instructions to patients

Patients and their carers must be instructed that ABSTRAL contains an active substance in an amount that can be fatal to a child and, therefore, to keep all tablets out of the reach and sight of children.

Due to the potentially serious undesirable effects that can occur when taking an opioid such as ABSTRAL, patients and their carers should be made fully aware of the importance of taking ABSTRAL correctly and what action to take should symptoms of overdose occur.

Hazardous and harmful use

ABSTRAL contains the opioid fentanyl (as citrate) and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed ABSTRAL at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed ABSTRAL.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and

advising the patient on the safe storage and proper disposal of any unused drug (see Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and Section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share ABSTRAL with anyone else.

Opioid-naive patients

ABSTRAL is contraindicated in non opioid-tolerant patients because of the risk of life-threatening respiratory depression (see 4.3 CONTRAINDICATIONS and Respiratory Depression).

Stabilisation of chronic opioid therapy

Before ABSTRAL therapy is initiated, it is important that the patient's long-acting opioid treatment used to control their persistent pain has been stabilised.

Ceasing opioids

For patients no longer requiring their chronic opioid therapy for the background cancer pain control, the ABSTRAL dose should be taken into consideration, before the gradual downward titration of other opioids, to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, ABSTRAL therapy can be discontinued immediately. The treatment by chronic opioids for the background cancer pain should be kept as prescribed. If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor.

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to treatment should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks. If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia

should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of opioids but the risk is greatest during initiation of therapy, following an increase in dose, when used in high doses especially high potency and modified release formulations, or in opioid naïve patients. Patients should be monitored closely for respiratory depression at these times. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients (see subsection on Special risk patients), and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma; other medical conditions predisposing them to respiratory depression such as myasthenia gravis) and in patients with hepatic or renal dysfunction (see subsection on Use in hepatic impairment and use in renal impairment). Opioids should be used with caution and with close monitoring in these patients (see 4.2 DOSE AND METHOD OF ADMINISTRATION). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see 4.3 CONTRADINDICATIONS).

In general, careful calculation of analgesic doses is required when changing opioids or switching from immediate release to modified release formulations (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION), together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response. It should be noted that ABSTRAL is not interchangeable with other fentanyl products. When prescribing or dispensing, do not convert patients on a microgram-per-microgram (1:1) basis from any other fentanyl products to ABSTRAL as this may lead to fatal overdose. If a change in opioid is required, it is essential that patients are again titrated with the new product (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Tolerance, dependence and withdrawal

ABSTRAL is contraindicated for treatment of non-cancer pain, non-breakthrough cancer pain and in patients who are not receiving opioids as background maintenance therapy. Use in these patients carries a risk of dependence (in addition to the risk of life-threatening respiratory depression). Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Neuroadaptation of the opioid receptors to repeated administration of opioids, including fentanyl, can produce tolerance and physical and/or psychological dependence. Iatrogenic addiction following therapeutic use of opioids is known to occur. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Upon cessation of treatment with ABSTRAL there should be no noticeable effects but drug withdrawal syndrome may occur, possible symptoms of which include: dysphoria,

restlessness/agitation, tremor, lacrimation, rhinorrhoea, yawning, sweating, chills, paleness, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

If discontinuation of all opioid therapy is required, ABSTRAL may be immediately ceased while the background opioid should be gradually tapered. The patient must be closely monitored by the doctor in order to avoid the possibility of abrupt withdrawal effects (see section on Ceasing opioids).

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, hypotension, coma and death (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Because of these risks, concomitant prescribing of ABSTRAL with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe ABSTRAL concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking ABSTRAL.

Accidental ingestion/exposure

Accidental ingestion or exposure of ABSTRAL, especially by children, can result in a fatal overdose of fentanyl. Patients and their caregivers should be given information on safe storage and disposal of unused ABSTRAL (see Section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and Section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL).

Special risk patients

Respiratory

The use of opioids is contraindicated in patients with severe respiratory disease, severe obstructive lung conditions, acute respiratory disease and respiratory depression (see Section 4.3 CONTRAINDICATIONS).

The risk of life-threatening respiratory depression is higher in elderly, frail or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma; other medical conditions predisposing them to respiratory depression such as myasthenia gravis) and in patients with hepatic or renal dysfunction (see subsection on Use in hepatic impairment and Use in renal impairment). ABSTRAL should be used with caution and with close monitoring in these patients, particularly during dose titration, because of the risk of further respiratory depression, which could lead to respiratory failure (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Head injuries and raised intracranial pressure

ABSTRAL should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of hypercapnia, such as those showing

evidence of raised intracranial pressure, reduced consciousness, coma, or brain tumours. In patients with head injuries, the clinical course may be masked by the use of opioids. In such a case, opioids should be used only if absolutely necessary.

Cardiovascular

Intravenous fentanyl has been shown to cause bradycardia. ABSTRAL should be used with caution in patients with previous or pre-existing bradyarrhythmias.

Hypovolaemia and hypotension

Care should be taken in treating patients with hypovolaemia and hypotension.

Serotonin Syndrome

Caution is advised when ABSTRAL is coadministered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Noradrenalin Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose range.

Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, treatment with ABSTRAL should be discontinued.

Mucositis

ABSTRAL has not been studied in patients with mouth wounds or mucositis. There may be a risk of increased systemic drug exposure in such patients; therefore, extra caution is recommended during dose titration.

Use in hepatic impairment

ABSTRAL should be administered with caution to patients with liver dysfunction, especially during the titration phase. The use of ABSTRAL in patients with hepatic impairment may increase the bioavailability of fentanyl and decrease its systemic clearance, which could lead to accumulation and increased and prolonged opioid effects.

Use in renal impairment

ABSTRAL should be administered with caution to patients with kidney dysfunction, especially during the titration phase. The use of ABSTRAL in patients with renal impairment may increase the bioavailability of fentanyl and decrease its systemic clearance, which could lead to accumulation and increased and prolonged opioid effects.

Use in the elderly

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life and they may be more sensitive to the active substance than younger patients. Elderly, cachectic or frail, or debilitated patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Paediatric use

ABSTRAL is not recommended for use in children and adolescents below 18 years since the appropriate posology and safety of ABSTRAL have not been established in this population. The opioid maintenance dose, which constitutes adequate opioid tolerance for the use of ABSTRAL, has not been investigated in children, nor has the adequate dosage been identified.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Inducers and Inhibitors of CYP3A4

Fentanyl is metabolised by CYP3A4. Active substances that inhibit CYP3A4 activity such as macrolide antibiotics (e.g. erythromycin), azole antifungal agents (e.g. ketoconazole, itraconazole) or certain protease inhibitors (e.g. ritonavir) may increase the bioavailability of fentanyl by decreasing its systemic clearance, potentially enhancing or prolonging opioid effects. Grapefruit juice is also known to inhibit CYP3A4. Co-administration with agents that induce CYP3A4 activity may reduce the efficacy of fentanyl. 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 therefore be given with caution to patients if administered concomitantly with CYP3A4 inhibitors and/or inducers.

Use with potent cytochrome P450 3A4 inducers may decrease the effect of fentanyl.

CNS Depressants

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, clonidine, centrally-active anti-emetics, gabapentinoids, cannabis and related substances may produce increased CNS depressant effects. Respiratory depression, hypotension, profound sedation, coma and death may occur.

Alcohol potentiates the sedative effects of morphine-based analgesics, therefore concomitant administration of alcoholic beverages or medicinal products containing alcohol with ABSTRAL is not recommended.

(see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol)

MAO Inhibitors

ABSTRAL is not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

Opioid Agonists/Antagonists

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.

Serotonergic Drugs

Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Noradrenalin Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In humans, the prolonged use of opioid analgesics may result in sexual dysfunction, infertility or impairment of fertility in both sexes, and menstrual disturbance in women. Impairment of fertility has been observed in female rats given 160 micrograms/kg/day subcutaneous fentanyl (no-effect dose not established) or 400 micrograms/kg/day intravenous fentanyl (no-effect dose 100 micrograms/kg/day). No effect was observed on the fertility of male rats given 400 micrograms/kg/day intravenous fentanyl.

Use in pregnancy

PREGNANCY CATEGORY C

Fentanyl crosses the placenta in humans (fetal blood concentrations about 40% of maternal blood concentrations). There are no adequate and well-controlled studies in pregnant women. ABSTRAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital abnormalities in infants born to women treated with fentanyl during pregnancy have been reported. Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioural changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In pregnant rats, fentanyl is embryocidal as evidenced by increased resorption at doses of 30 micrograms/kg/day intravenously or 160 micrograms/kg/day or greater subcutaneously. Intravenous administration to rats at 30 micrograms/kg/day during organogenesis was associated with prolonged delivery time and increased postnatal mortality of offsprings. There was no effect on embryofetal development when rats received fentanyl at subcutaneous doses up to 500 micrograms/kg/day throughout gestation, and no evidence of teratogenicity in rabbits administered fentanyl at intravenous doses up to 400 micrograms/kg/day during organogenesis. The significance of these findings for potential human risk is unknown.

Use in lactation

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

However, fentanyl may impair the mental or physical ability to perform potentially hazardous tasks such as driving or operating machinery. Patients should be advised not to drive or operate machinery if they become dizzy or drowsy or experience blurred or double vision while taking ABSTRAL.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety assessment showed that the majority of patients in Phase III studies (73.3%) experienced at least one Treatment Emergent Adverse Event (TEAE), which is to be expected considering the patient population and a long-term period of observation of up to 12 months. There was no evidence of any TEAEs becoming more prevalent or severe over time. 31.3% of patients experienced TEAEs that were considered product-related by the investigator. The most common of these were nausea, somnolence and vomiting, all of which are known undesirable effects of opioids, and in keeping with the findings of previous clinical studies with ABSTRAL. Serious TEAEs were experienced by 18.3% of patients; only one of these (affect lability) was considered related to study medication.

Undesirable effects typical of opioids are to be expected with ABSTRAL; they tend to decrease in intensity with continued use. The most serious potential adverse reactions associated with opioid use are respiratory depression (which could lead to respiratory arrest), hypotension and shock.

The clinical trials of ABSTRAL were designed to evaluate safety and efficacy in treating patients with breakthrough cancer pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain. Therefore it is not possible to definitively separate the effects of ABSTRAL alone.

The most frequently observed adverse reactions with ABSTRAL include typical opioid adverse reactions, such as nausea, constipation, somnolence and headache.

The following adverse reactions have been reported with ABSTRAL and/or other fentanyl-containing compounds during clinical studies and from post-marketing experience. They are listed below by system organ class and frequency (very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1,000 to < 1/100; not known (cannot be estimated from available data)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Tabulated Summary of Adverse Reactions with ABSTRAL and/or other fentanyl-containing compounds

System Organ Class	Adverse Reaction by Frequency			
	Very common ≥ 1/10	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1000 to <1/100**	**Not known (cannot be estimated from available data)**
Immune system disorders			Hypersensitivity	
Metabolism and nutrition disorders			Anorexia Decreased appetite	
Psychiatric disorders			Depression Paranoia Confusional state Disorientation Mental status changes Anxiety Euphoric mood Dysphoria Emotional lability Disturbance in attention Insomnia	Hallucination Drug dependence (addiction) Drug abuse Delirium
Nervous system disorders		Dizziness Headache Somnolence	Amnesia Parosmia Dysgeusia Tremor Lethargy Hypoasthesia Sleep disorder	Convulsion Depressed level of consciousness Loss of consciousness
Eye disorders			Vision blurred	
Cardiac disorders			Tachycardia Bradycardia	
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Oropharyngeal pain Throat tightness	Respiratory depression

System Organ Class	Adverse Reaction by Frequency			
	Very common ≥ 1/10	**Common ≥ 1/100 to <1/10**	**Uncommon ≥ 1/1000 to <1/100**	**Not known (cannot be estimated from available data)**
Gastrointestinal disorders	Nausea	Stomatitis Vomiting Constipation Dry mouth	Mouth ulceration Gingival ulceration Lip ulceration Impaired gastric emptying Abdominal pain Dyspepsia Stomach discomfort Tongue disorder Aphthous stomatitis	Swollen tongue Diarrhoea
Skin and subcutaneous tissue disorders		Hyperhidrosis	Skin lesion Rash Pruritus allergic Pruritus Night sweats Increased tendency to bruise	Urticaria
Musculoskeletal and connective tissue disorders			Arthralgia Musculoskeletal stiffness Joint stiffness	
Reproductive system and breast disorders			Erectile dysfunction	
General disorders and administration site conditions		Fatigue	*Drug withdrawal syndrome Asthenia Malaise	Flushing and hot flush Peripheral oedema Pyrexia
Injury, poisoning and procedural complications			Accidental overdose	Fall

* Opiate withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating have been observed with transmucosal fentanyl

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

The symptoms of fentanyl overdose are an extension of its pharmacological actions, the most serious effect being respiratory depression, which may lead to respiratory arrest. Coma is also known to occur.

Management of opioid overdose in the immediate term includes removal of any remaining ABSTRAL sublingual tablets from the mouth, physical and verbal stimulation of the patient and an assessment of the level of consciousness. A patent airway should be established and maintained. If necessary an oropharyngeal airway or endotracheal tube should be inserted, oxygen administered and mechanical ventilation initiated, as appropriate. Adequate body temperature and parenteral fluid intake should be maintained.

For the treatment of accidental overdose in opioid-naïve individuals, naloxone or other opioid antagonists should be used as clinically indicated and in accordance with their Product Information. Repeated administration of the opioid antagonist may be necessary if the duration of respiratory depression is prolonged.

Care should be taken when using naloxone or other opioid antagonists to treat overdose in opioid-maintained patients, due to the risk of precipitating an acute withdrawal syndrome.

If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

Muscle rigidity interfering with respiration has been reported with fentanyl and other opioids. In this situation, endotracheal intubation, assisted ventilation and administration of opioid antagonists as well as muscle relaxants may be requested.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fentanyl is a potent μ-opioid analgesic with rapid onset of analgesia and short duration of action. Fentanyl is approximately 100-fold more potent than morphine as an analgesic. Secondary effects of fentanyl on the central nervous system (CNS), respiratory and gastro-intestinal function are typical of opioid analgesics and are considered to be class effects. These can include respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

The analgesic effects of fentanyl are related to the blood level of the active substance; in opioid-naïve patients, minimum effective analgesic serum concentrations of fentanyl range from 0.3 to 1.2 ng/mL, while blood levels of 10 to 20 ng/mL produce surgical anaesthesia and profound respiratory depression.

Fentanyl, in common with all μ-opioid receptor agonists, produces dose-dependent respiratory depression. This risk is higher in opioid-naïve subjects than in patients experiencing severe pain or receiving chronic opioid therapy. Long-term treatment with opioids typically leads to development of tolerance to their secondary effects.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract leading to a prolongation in gastrointestinal transit time, which may be responsible for the constipating effect of fentanyl.

Clinical Trials

Fentanyl citrate has been used extensively for pain relief, including cancer patients, and a significant body of research has been published in the scientific literature.

The efficacy of ABSTRAL was investigated in Study EN3267-005, a randomised, double-blind, placebo-controlled, multicenter phase III study in 131 opioid-tolerant cancer patients with breakthrough pain. All patients (n=131) were receiving a stable, fixed-schedule oral opioid regimen equivalent to 60 to 1000 mg of oral morphine per day or transdermal fentanyl therapy equivalent to 50 to 300 micrograms/h; were on a stable dose of opioid medication for relief of breakthrough pain; and were experiencing at least one but not more than 4 episodes of breakthrough pain per day. Pre-emptive use of ABSTRAL for predictable pain episodes was not investigated in the clinical trials.

Patients were titrated to a single effective dose of ABSTRAL for adequate treatment of their breakthrough cancer pain in an initial open-label phase. Patients who were successfully titrated were then included in a double-blind, randomised, placebo-controlled phase of up to 2 weeks, during which 10 episodes of breakthrough cancer pain were treated with ABSTRAL (7 doses) or placebo (3 doses). Patients who completed the double-blind phase elected to continue in an open-label extension phase using ABSTRAL to treat breakthrough cancer pain episodes for up to 12 months.

Open-label titration identified a successful dose of ABSTRAL, within the range of 100 to 800 micrograms. A “successful” dose was defined as the one, single dosage strength of ABSTRAL that successfully treated all breakthrough cancer pain episodes that occurred for two consecutive days with tolerable side effects. Of the 131 patients enrolled, 53 (40.5%) discontinued during the titration period.

The final titrated dose of ABSTRAL for breakthrough cancer pain was not predictable from the background opioid dose underlying the need for individual titration starting at 100 micrograms.

The interim analysis of efficacy became the primary analysis because it lead to the double-blind treatment phase of the study being terminated in accordance with the predefined stopping rules, after which patients proceeded directly from the titration period to the open-label long-term extension.

The mean age of subjects in the intention-to-treat (ITT) population (n=131) was 55.0 years (range 21 to 80 years) with 54.2% female and 45.8% male.

The primary efficacy endpoint was the Sum of Pain Intensity Difference (SPID) from Baseline to 30 minutes after treating breakthrough cancer pain episodes with study medication. The secondary objectives were to compare the efficacy of ABSTRAL with that of placebo in treating breakthrough cancer pain (BTcP) episodes in opioid-tolerant cancer patients for 1) Pain Intensity Difference (PID) and Pain Relief (PR) at time points 10, 15, 30 and 60 min; patient global evaluation of study medication, and the use of rescue medication; and 2) to evaluate the safety and tolerability of ABSTRAL in treating BTcP episodes in opioid-tolerant cancer patients, as measured by the occurrence of adverse events (AEs) and withdrawals because of AEs.

ABSTRAL was found to be superior to placebo in treating breakthrough cancer pain as measured by SPID over the first 30 minutes of a breakthrough episode (49.3, 35.23 respectively, p=0.0004). The difference of least squares mean between the treatments was 14.08 (95% CI: 6.515, 21.637).

The difference in SPID reached statistical significance (p=0.006) as early as 10 minutes postdose and the difference continued to be statistically significant through all time points thereafter until the final assessment at 60 minutes post-dose (Figure 1).

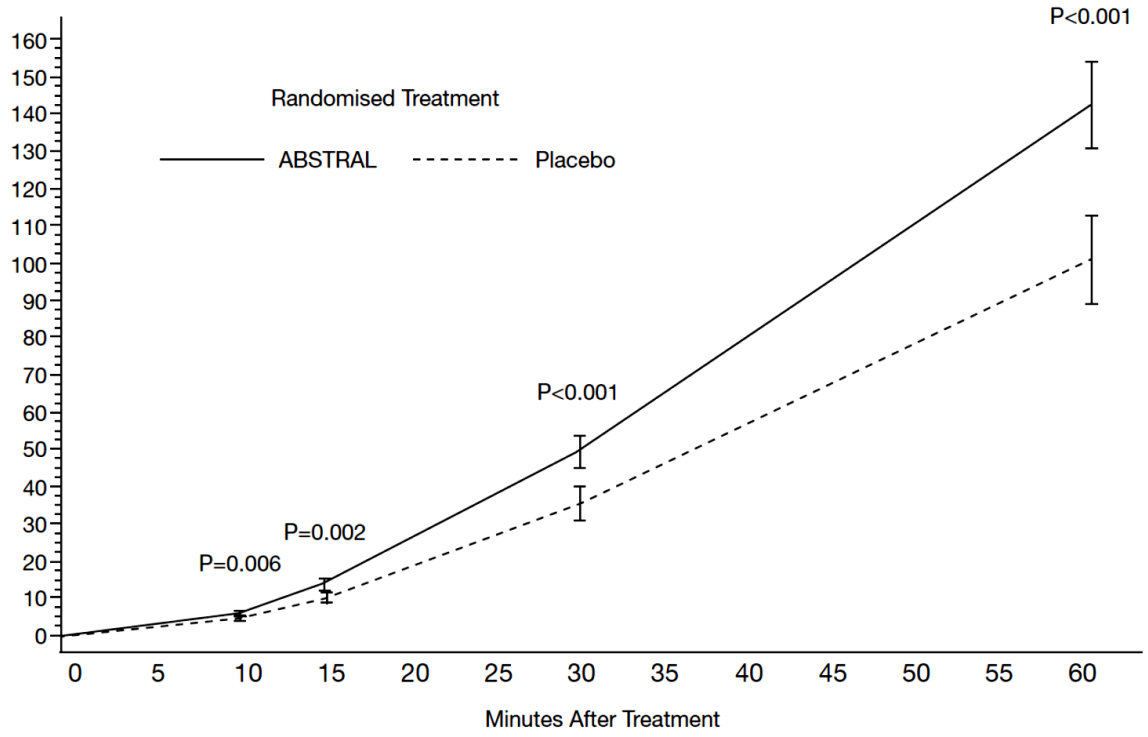


Figure 1: Mean Sum Pain Intensity Difference (SPID) for ABSTRAL Compared with Placebo

ABSTRAL was also shown to provide improved reduction in Pain Intensity Difference (PID), a pre-specified secondary endpoint, from the first measured time point (10 minutes) that was significantly different to placebo (1.16 vs. 0.88 respectively; p=0.0055). The statistically significant difference was maintained to at least 60 minutes (Figure 2).

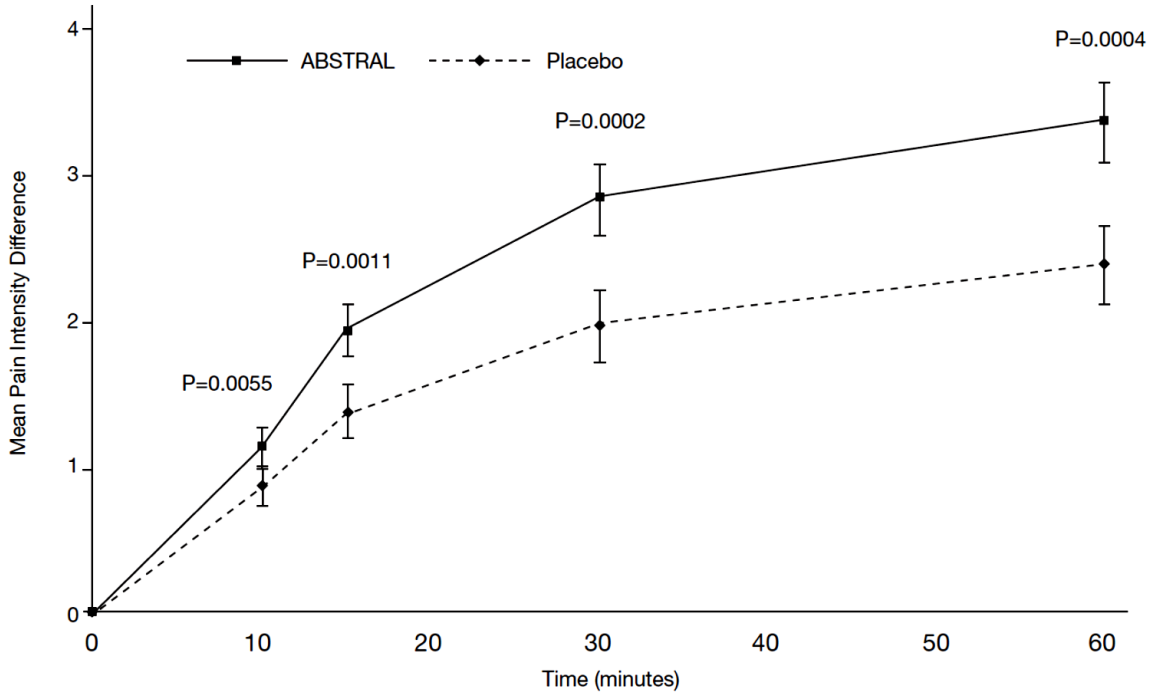


Figure 2: **Mean Pain Intensity Difference from baseline (± SE) for ABSTRAL Compared with Placebo (measured by a 0-10 Lickert scale)**

Similarly, ABSTRAL provided statistically significantly greater pain relief, compared with placebo, from 10 min postdose (pre-specified secondary endpoint) and throughout the assessment period (p=0.049; Figure 3). Clinically significant differences between ABSTRAL and placebo were apparent approximately 30 minutes after dosing and were maintained for approximately 60 minutes after dosing.

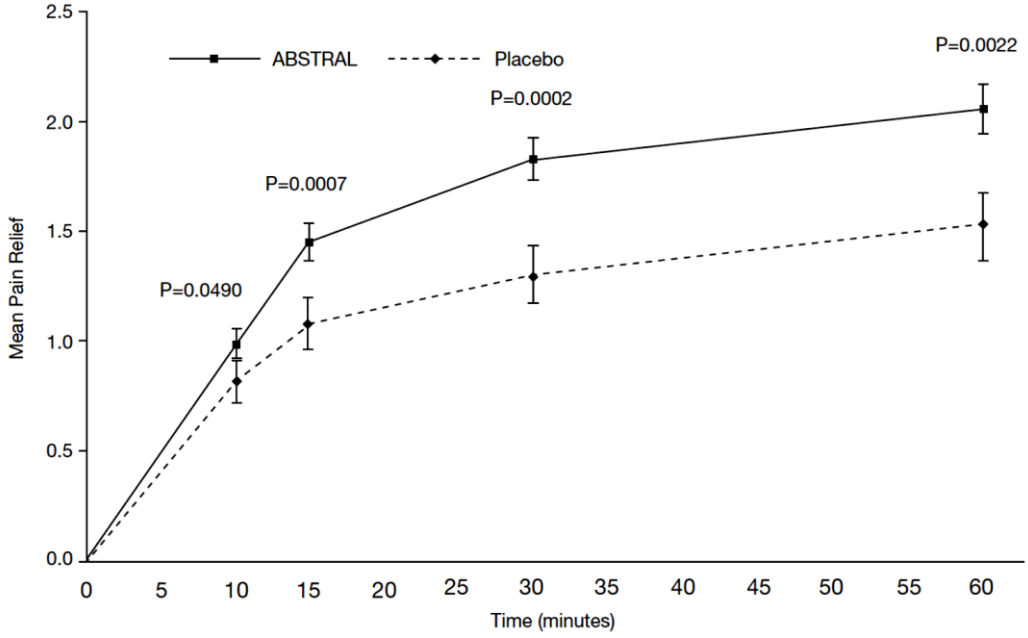


Figure 3: **Mean pain relief over time for breakthrough cancer pain episodes treated with ABSTRAL and placebo (interim ITT, n=61). Error bars represent Standard Error.**

The efficacy of ABSTRAL compared with placebo was examined across gender, age, and dose subgroups, as well as by the type of opioid medication patients used for their fixed-schedule analgesic treatment for chronic pain (Table 2).

Table 2 - Mean Sum of Pain Intensity Difference (SPID) at 30 and 60 Minutes after Treatment by Gender, Age, Dose, and Type of Opioid Medication (Study EN3267-005, ITT Population)

	SPID 30				SPID 60			
Demographics and Baseline Characteristics	**N**	**ABSTRAL Mean (SD)**	**N**	**Placebo Mean (SD)**	**N**	**ABSTRAL Mean (SD)**	**N**	**Placebo Mean (SD)**
Gender								
Male	30	48.06 (32.23)	27	36.65 (37.50)	30	131.68 (75.61)	27	99.47 (86.58)
Female	31	50.85 (33.68)	30	36.62 (42.23)	31	153.88 (90.68)	30	109.03 (118.21)
Age group								
18-64	52	51.25 (32.84)	49	36.55 (39.67)	52	145.66 (83.30)	49	100.64 (100.35)
65-74	8	37.32 (33.60)	7	35.19 (45.68)	8	121.25 (93.22)	7	124.95 (136.77)
>74	1	54.49	1	51.00	1	176.07	1	150.67
Dose group								
Low (100-400 micrograms)	33	53.07 (21.91)	31	40.60 (41.96)	33	152.16 (80.16)	31	114.03 (111.68)
High (600-800 micrograms)	28	45.24 (35.86)	26	31.91 (37.09)	28	132.12 (87.82)	26	93.14 (94.03)
Type of opioid medication								
Oral	60	48.60 (32.29)	56	35.06 (38.22)	60	140.54 (82.18)	56	99.77 (98.17)
Transdermal	20	40.07 (20.52)	20	27.18 (31.39)	20	127.53 (55.02)	20	85.15 (86.78)
Other	1	34.86	1	22.17	1	105.43	1	66.67

NOTE: SPID is calculated as the area under a patient's PID curve from each BTcP episode treated with study medication and then averaged across episodes by treatment group.

Abbreviation: BTcP = breakthrough cancer pain; SD = standard deviation; SPID = sum of pain intensity difference.

Results of the subgroup analyses of the SPID for the ITT population consistently favoured the ABSTRAL treatment group compared with the placebo treatment group regardless of gender or age. Higher mean SPIDs were found at 30 and 60 minutes after treatment with low (100 to 400 micrograms) or high (600 to 800 micrograms) doses, indicating that once titration to an appropriate dose was achieved, the response to ABSTRAL was similar across dose groups. In addition, higher mean SPIDs were recorded at both 30 and 60 minutes after treatment with ABSTRAL regardless of the type of background opioid medication used to treat chronic cancer pain.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Fentanyl is a highly lipophilic drug absorbed very rapidly through the oral mucosa and more slowly through the gastrointestinal tract. Orally administered fentanyl undergoes pronounced hepatic and intestinal first-pass effects.

ABSTRAL is a quick-dissolving sublingual tablet formulation. Rapid absorption of fentanyl occurs over about 30 minutes following administration of ABSTRAL. The absolute bioavailability of ABSTRAL has been calculated to be 54%. Mean maximal plasma concentrations of fentanyl range from 0.2 to 1.5 ng/mL (after administration of 100 to 800 micrograms ABSTRAL) and are reached within 22.5 to 240 minutes.

Distribution

About 80-85% of fentanyl is bound by plasma proteins, mainly α1-glycoprotein and to a lesser extent albumin and lipoprotein. The volume of distribution of fentanyl at steady state is about 3-6 L/kg.

Metabolism

Fentanyl is metabolised primarily via CYP3A4 to a number of pharmacologically inactive metabolites, including norfentanyl.

Excretion

Within 72 hours of intravenous fentanyl administration around 75% of the dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites. Total plasma clearance of fentanyl is about 0.5 L/h/kg. After ABSTRAL administration, the mean elimination half-life of fentanyl is about 7 hours (range 3 to 12.5 hours) and the terminal half-life is about 20 hours (range 11.5 to 25 hours).

The pharmacokinetics of ABSTRAL have been shown to be dose proportional over the dose range of 100 to 800 micrograms. Pharmacokinetic studies have shown that multiple tablets are bioequivalent to single tablets of the equivalent dose.

Renal/hepatic impairment

Impaired hepatic or renal function could cause increased serum concentrations. Elderly, cachectic or generally impaired patients may have a lower fentanyl clearance, which could cause a longer terminal half-life for the compound (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test, mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA synthesis in rat hepatocytes, mammalian cell transformation assay). The metabolite despropionylfentanyl was negative in assays for reverse mutation in bacteria and chromosomal damage in human lymphocytes. The genotoxic potential of fentanyl is considered to be low.

Carcinogenicity

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) with fentanyl did not reveal any findings indicative of oncogenic potential. Evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Store in the original blister package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

ABSTRAL is supplied in child-resistant foil blister packs of 10 sublingual tablets.

Each blister pack is packaged in cartons of 10 or 30 sublingual tablets.

The packaging is colour-coded for each ABSTRAL sublingual tablet strength.

Not all pack sizes may be marketed.

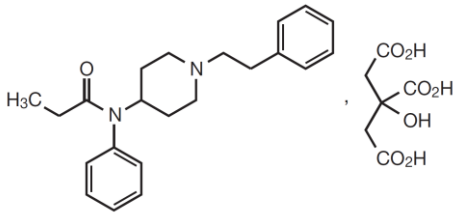
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Fentanyl citrate is a highly lipophilic white or almost white powder that is freely soluble in organic solvents (logPoctanol/water = 2.98) and soluble in water (1:40). The dissolution rate of fentanyl citrate is promoted by the use of a micronised grade.

Chemical Structure



Chemical name (IUPAC): *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate
CAS number: 990-73-8
Molecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$
Molecular weight: 528.6 (free base 336.5)
Pharmacotherapeutic group: Phenylpiperidine derivatives
ATC Code: N02AB03

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 (CONTROLLED DRUG)

8. SPONSOR

A. Menarini Australia Pty Ltd
Level 8, 67 Albert Avenue
Chatswood, NSW 2067
Australia
Phone: 1800 644 542

9. DATE OF FIRST APPROVAL

22 August 2013

10. DATE OF REVISION

21 July 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Header	Addition of Boxed Warning consequent of TGA opioid reforms
4.3	Addition of severe respiratory disease, acute respiratory and use in patients for non-breakthrough cancer pain as contraindications, consequent of TGA opioid reforms.
4.4	Multiple changes consequent of TGA opioid reform, including: Hazardous and harmful use, Ceasing Opioids, Respiratory depression, Risks from concomitant use of benzodiazepines or other CNS depressants including alcohol, Tolerance, dependence and withdrawal, Accidental ingestion/ exposure, and Hyperalgesia.
4.8	Addition of delirium as post-marketing adverse drug reaction with unknown frequency.