ABSTRAL® (fentanyl citrate) sublingual tablets

PRODUCT INFORMATION

NAME OF THE MEDICINE

Fentanyl citrate is known chemically as N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate. The molecular formula is C_{22}H_{28}N_{2}O, C_{6}H_{8}O_{7} and the molecular weight is 528.6 (free base 336.5).

Structural formula:

![Structural formula](attachment:image)

CAS Registry: 990-73-8

DESCRIPTION

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

ABSTRAL sublingual tablets contain the following excipients: mannitol, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate.

PHARMACOLOGY

Fentanyl citrate belongs to the pharmacotherapeutic group: Phenylpiperidine derivatives (ATC code: N02AB03)

Pharmacodynamics

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 central nervous system (CNS), respiratory and gastrointestinal function are typical of opioid analgesics and are considered to be class effects.

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 0.3-1.2 ng/mL, while blood levels of 10-20 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.
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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.

**Pharmacokinetics**

*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 µg 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 main elimination half-life of fentanyl is about 7 hours (range 3-12.5 hours) and the terminal half-life is about 20 hours (range 11.5-25 hours).

The pharmacokinetics of Abstral have been shown to be dose proportional over the dose range of 100 to 800 µg. 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
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cause a longer terminal half-life for the compound (see also PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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.

In patients with chronic cancer pain on stable maintenance doses of opioids, statistically significant improvement in pain intensity difference was seen with Abstral versus placebo from 10 minutes after administration onwards (see Figure 1 below), with a significantly lower need for rescue analgesic therapy.

![Figure 1](image)

**Figure 1** Mean Pain Intensity Difference from baseline (± SE) for Abstral Compared with Placebo (measured by a 0-10 Lickert scale)

The safety and efficacy of Abstral have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Pre-emptive use of ABSTRAL for predictable pain episodes was not investigated in the clinical trials.

ABSTRAL has been investigated in clinical trials involving treating a total of 393 subjects, of which 172 were opioid-tolerant cancer patients experiencing breakthrough pain. Efficacy has been specifically assessed in a double-blind, randomised, placebo-controlled Phase III study involving the treatment of 131 opioid-tolerant cancer patients experiencing breakthrough pain.

The Phase III study (Study EN3267-005) was a double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of ABSTRAL for the treatment of breakthrough pain in opioid tolerant cancer patients followed by an up to 12-month non-randomized, open-label extension to assess long-term safety.
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The Phase III study consisted of three parts. Patients were initially titrated up to an effective and tolerable dose of ABSTRAL within the range 100 to 800 µg, and were then entered into the randomised placebo controlled period, during which patients treated 10 episodes of breakthrough cancer pain (BTcP) (7 with ABSTRAL and 3 with placebo). This was followed by an open-label extension during which patients continued to take ABSTRAL for up to 12 months.

A total of 131 opioid-tolerant patients with cancer-related pain were enrolled in this study. Of these, 78 (60%) achieved a successful dose during the titration period. The titration schedule and doses provided appeared suitable for this patient group. Sixty-six patients entered the double-blind treatment period, of whom 61 were included in the intent-to-treat (ITT) population of the interim analysis of efficacy. 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. A total of 72 patients entered the open-label long-term extension (60 who completed double-blind treatment and 12 directly from the open-label titration period); 25 patients completed the 12-month open-label extension.

The primary objective was to compare the efficacy of ABSTRAL with that of placebo in BTcP episodes in opioid-tolerant cancer patients who were using stable doses of opioid medication, as measured by the sum of pain intensity difference (SPID) from Baseline to 30 minutes after dosing.

The secondary objectives were 1) to compare the efficacy of ABSTRAL with that of placebo in treating BTcP episodes in opioid-tolerant cancer patients, as measured by ratings of pain intensity, pain relief (PR), 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.

The primary efficacy endpoint indicated that episodes treated with ABSTRAL showed a significantly better SPID compared with episodes treated with placebo at 30 minutes after treatment (P = 0.0004). See Table 1 below:
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Table 1: Mean Sum of Pain Intensity Difference at 30 Minutes After Treatment During the Double-blind Treatment Phase (Study EN3267-005, ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>ABSTRAL (N = 61)</th>
<th>Placebo (N = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPID at 30 minutes</strong>a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>49.5 (32.7)</td>
<td>36.6 (39.7)</td>
</tr>
<tr>
<td>Median</td>
<td>39.3</td>
<td>28.3</td>
</tr>
<tr>
<td>Range</td>
<td>6.7-138.8</td>
<td>-17.5-150.8</td>
</tr>
<tr>
<td><strong>Treatment comparison vs placebo</strong>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean (SE)</td>
<td>49.30 (4.3)</td>
<td>35.23 (4.3)</td>
</tr>
<tr>
<td>LS mean difference</td>
<td>14.08</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(6.515, 21.637)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

a The SPID was 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.
b The analysis used an analysis of variance model with fixed effects for treatment, pooled centre, and sequence, and random effect for patient. The observed margins option in the LSMEANS statement assigned weights based on all the covariates in the model except for treatment (ie, sequence and pooled centre).

Abbreviations: BTcP = breakthrough cancer pain; CI = confidence interval; ITT = intent to treat; LS = least squares; PID = pain intensity difference; SD = standard deviation; SE = standard error; SPID = sum of pain intensity difference

ABSTRAL produced a statistically significant improvement over placebo for up to 12 months in the treatment of BTcP episodes in opioid-tolerant cancer patients from 10 minutes after dose administration. Clinically significant differences between ABSTRAL and placebo were apparent approximately 30 minutes after dosing and were maintained for approximately 60 minutes after dosing.

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.

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 depression or severe obstructive lung conditions.
- Use in patients not receiving opioid maintenance therapy for cancer related pain.

PRECAUTIONS

Instructions to patients
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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 therapy 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.

Opioid-naive patients

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

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.

Tolerance, dependence and withdrawal

ABSTRAL is contraindicated for treatment of non-cancer-related pain. Use in patients who are not receiving maintenance opioid therapy for cancer-related pain 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.

Upon repeated administration of opioids such as fentanyl, tolerance and physical and/or psychological dependence may develop. Iatrogenic addiction following therapeutic use of opioids is rare.

There should be no noticeable effects on cessation of treatment with ABSTRAL, but possible symptoms of withdrawal are anxiety, tremor, sweating, paleness, nausea and vomiting.

Special risk patient

Respiratory

In common with all opioids, there is a risk of clinically significant respiratory depression associated with the use of ABSTRAL. Particular caution should be exercised during dose titration with ABSTRAL in patients with chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression (e.g. myasthenia gravis) because of the risk of further respiratory depression, which could lead to respiratory failure.

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 hyperkapnia, such as those showing evidence of raised intracranial pressure, reduced consciousness, coma or brain tumours. In
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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 bradyarrhythmias.

Hypovolaemia and hypotension

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

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 debilitated patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Hepatic and renal impairment

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

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 and therefore extra caution is recommended during dose titration.

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 µg/kg/day subcutaneous fentanyl (no-effect dose not established) or 400 µg/kg/day intravenous fentanyl (no-effect dose 100 µg/kg/day). No effect was observed on the fertility of male rats given 400 µg/kg/day intravenous fentanyl.

Use in 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
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depression, behavioural changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

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

Use in lactation

Administration of fentanyl to female rats from early gestation to weaning was associated with reduced early postnatal survival. This could be a direct effect on the pups or secondary to maternal toxicity.

Use in children and adolescents

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.

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

In a two year study in rats, there was no evidence of carcinogenicity following daily subcutaneous administration of fentanyl at the maximum tolerated dose.

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.
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INTERACTIONS WITH OTHER MEDICINES

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. Fentanyl should therefore be given to patients with caution if administered concomitantly with CYP3A4 inhibitors.

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

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 and related substances may produce increased CNS depressant effects. Respiratory depression, hypotension and profound sedation 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.

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.

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.

ADVERSE 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 experience 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
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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.

Tabulated Summary of Adverse Reactions with Abstral:

Adverse reactions from patient safety and efficacy studies with ABSTRAL with a suspected relationship to treatment, and from post-marketing experience are listed below by system organ class and frequency (very common \(\geq 1/10\); common \(\geq 1/100\) to < \(1/10\); uncommon \(\geq 1/1,000\) to < \(1/100\); not known (cannot be estimated from available data)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
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<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction by Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common ≥ 1/10</td>
</tr>
<tr>
<td></td>
<td>Common ≥ 1/100 to &lt;1/10</td>
</tr>
<tr>
<td></td>
<td>Uncommon ≥ 1/1000 to &lt;1/100</td>
</tr>
<tr>
<td></td>
<td>Not known (cannot be estimated from available data)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia Decreased appetite</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression Paranoia Confusional state Disorientation Mental status changes Anxiety Euphoric mood Dysphoria Emotional lability Disturbance in attention</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness Headache Somnolence</td>
</tr>
<tr>
<td></td>
<td>Amnesia Parosmia Dysgeusia Tremor Lethargy Hypoaesthesia Insomnia Sleep disorder</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia Bradycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea Oropharyngeal pain Throat tightness</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea Stomatitis Vomiting Constipation Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Mouth ulceration Gingival ulceration Lip ulceration Impaired gastric emptying Abdominal pain Dyspepsia Stomach discomfort Tongue disorder</td>
</tr>
<tr>
<td></td>
<td>Swollen tongue*</td>
</tr>
</tbody>
</table>
ABSTRAL® (fentanyl citrate) sublingual tablets

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction by Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common (\geq \frac{1}{10})</td>
</tr>
<tr>
<td>Aphthous stomatitis</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>Skin lesion</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Pruritus allergic</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Night sweats</td>
</tr>
<tr>
<td></td>
<td>Increased tendency to bruise</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Musculoskeletal stiffness</td>
</tr>
<tr>
<td></td>
<td>Joint stiffness</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Drug withdrawal syndrome</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td></td>
</tr>
</tbody>
</table>

* Observed in post-marketing experience only.

**DOSAGE AND 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 oral morphine per day, 50 µg transdermal fentanyl per hour, 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.
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Dose titration

The object of dose titration is to identify an optimal maintenance dose for ongoing treatment of breakthrough 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 optimal dose of ABSTRAL will be determined by upward titration, on an individual patient basis. Several doses are available for use during the dose titration phase. The initial dose of ABSTRAL used should be 100 µg, titrating upwards as necessary through the range of available dosage strengths.

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

Switching from other fentanyl containing products to ABSTRAL must not occur at a 1:1 ratio because of different absorption profiles, see Titration in patients switching between immediate-release fentanyl containing products below.

The following dose regimen is recommended for titration, although in all cases the physician should take into account the clinical need of the patient, age and concomitant illness.

All patients must start therapy with a single 100 µg sublingual tablet. If adequate analgesia is not obtained within 30 minutes of administration of a single sublingual tablet, a supplemental (second) 100 µg sublingual tablet may be administered. If adequate analgesia is not obtained within 15-30 minutes of the first dose an increase in dose to the next highest dose should be considered for the next episode of breakthrough pain (Refer to figure below). Dose escalation should continue in a stepwise manner until adequate analgesia is achieved. The strength for the supplemental (second) dose should be increased from 100 to 200 µg at doses of 400 µg and higher. This is illustrated in the schedule below. No more than two (2) doses should be administered for a single episode of breakthrough pain during this titration phase.
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Starting dose (100 µg)

Adequate pain relief achieved within 30 minutes?

Yes

Take a second dose (See table to determine strength of second dose)

Use this dose for subsequent breakthrough pain

No

Increase first dose to next higher strength for next breakthrough pain episode

<table>
<thead>
<tr>
<th>Strength (µg) of first sublingual dose per episode of breakthrough pain</th>
<th>Strength (µg) of supplemental (second) sublingual tablet to be taken 15–30 minutes after first dose, if required</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>400</td>
<td>200</td>
</tr>
</tbody>
</table>

If adequate analgesia is achieved at the higher dose, but undesirable effects are considered unacceptable, an intermediate dose (using the 100 µg sublingual tablet where appropriate) may be administered.

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. Doses higher than 800 µg have not been evaluated in clinical studies.

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 process.

During titration patients should wait at least 2 hours before treating another episode of breakthrough pain with Abstral.

**Titration in patients switching between immediate-release fentanyl containing products**
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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 product is re-titrated from the initial starting dose. When prescribing, do not convert patients on a microgram per microgram 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 pain, including intranasal formulations, it is essential that patients are again titrated with the new product, and not switched on a dose-for-dose (microgram-for-microgram) basis.

Maintenance therapy

Once an appropriate dose has been established, which may be more than one tablet, patients should be maintained on this dose and should limit consumption to a maximum of four ABSTRAL doses per day.

During the maintenance period patients should wait at least 2 hours before treating another episode of breakthrough pain with Abstral.
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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 episodes of breakthrough pain are experienced per day over a period of more than four consecutive days, then the dose of the long acting opioid used for persistent pain should be re-evaluated. If the long acting opioid or dose of long acting opioid is changed the ABSTRAL dose should be re-evaluated and re-titrated 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 health professional.

Discontinuation of therapy

For patients no longer requiring any opioid therapy, the ABSTRAL dose should be taken into consideration before a gradual downward titration of opioids to minimise 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 may usually be discontinued immediately.

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 PRECAUTIONS).

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 PRECAUTIONS).

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.

OVERDOSAGE

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.
ABSTRAL® (fentanyl citrate) sublingual tablets

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.

PRESENTATION AND STORAGE CONDITIONS

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

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

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

ABSTRAL is supplied in child resistant foil blister packs of 10 or 30 sublingual tablets. The packaging is colour-coded for each ABSTRAL sublingual tablet strength. Not all pack sizes may be marketed.

Store below 25°C.

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

NAME AND ADDRESS OF THE SPONSOR

A.Menarini Australia Pty Ltd
Level 8, 67 Albert Avenue
Chatswood, NSW 2067
Australia

POISON SCHEDULE OF THE MEDICINE
ABSTRAL® (fentanyl citrate) sublingual tablets

S8
ABSTRAL® (fentanyl citrate) sublingual tablets

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 August 2013