PRODUCT MONOGRAPH

[N]ABSTRAL®

Fentanyl citrate sublingual tablets

100 µg, 200 µg, 300 µg, 400 µg, 600 µg and 800 µg fentanyl as fentanyl citrate

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Sublingual	Sublingual tablets containing: 100 micrograms fentanyl (as 157.1 mcg fentanyl citrate), 200 micrograms fentanyl (as 314.2 mcg fentanyl citrate) 300 micrograms fentanyl (as 471.3 mcg fentanyl citrate) 400 micrograms fentanyl (as 628.4 mcg fentanyl citrate) 600 micrograms fentanyl (as 942.6 mcg fentanyl citrate) 800 micrograms fentanyl (as 1257 mcg fentanyl citrate)	Croscarmellose sodium, magnesium stearate, mannitol, silicified microcrystalline cellulose

INDICATIONS AND CLINICAL USE

Adults

ABSTRAL (fentanyl citrate sublingual tablet) is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving, and who are tolerant to, opioid therapy for their persistent baseline cancer pain.

Patients considered opioid tolerant are those who are taking at least 60 mg/day morphine equivalents for a week or longer.

All patients starting treatment with Abstral must begin with titration from the 100 µg dose (see **DOSAGE AND ADMINISTRATION**).

This product must not be used in opioid non-tolerant patients because life-threatening respiratory depression could occur in patients not taking chronic opiates. For this reason, Abstral is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

Abstral is intended to be used only by healthcare professionals who are knowledgeable of, and skilled in the use of opioids to treat cancer pain.

Geriatrics:

Elderly patients may be more sensitive to the effects of fentanyl, compared with the younger population. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects. Therefore, exercise caution when titrating Abstral in elderly patients.

Pediatrics (< 18 years of age):

Abstral is not indicated in children under the age of 18 years, as dosage requirements for the safe and effective use of Abstral have not been established for this patient population.

CONTRAINDICATIONS

Because serious or life-threatening hypoventilation could occur, ABSTRAL (fentanyl citrate sublingual tablet) is contraindicated in:

- Opioid non-tolerant patients (e.g. use in acute or post-operative pain, headache/migraine, dental pain, or use in the emergency room);
- Severe respiratory depression or severe obstructive lung conditions

See boxed Serious Warnings and Precautions for details regarding proper patient selection.

Abstral is also contraindicated in patients with known intolerance or hypersensitivity to fentanyl or to any ingredient in the formulation or component of the container. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of this product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

WARNINGS
IMPORTANCE OF PROPER PATIENT SELECTION, and POTENTIAL FOR ABUSE

Abstral (fentanyl citrate sublingual tablet) contains fentanyl, an opioid agonist and a Schedule 1 controlled substance, with an abuse liability similar to other opioid analgesics. Abstral can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Abstral in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

ABSTRAL is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of opioids to treat cancer pain.

ABSTRAL is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age or older, who are already receiving and who are tolerant to opioid therapy for their persistent baseline cancer pain. Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ABSTRAL is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis.

Fentanyl products which are designed to manage breakthrough pain, including ABSTRAL, should not be used in patients who are receiving partial opioid agonists such as buprenorphine or agents with some opioid effects such as tramadol, as the safety of their concomitant use has not been established.

ABSTRAL is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ABSTRAL. If patients are using other opioid-containing products for breakthrough pain, they may be started on Abstral at the initial dose of 100 mcg.

Regardless of the opioid dose used for the baseline cancer pain, patients beginning treatment with ABSTRAL must begin with titration from the 100 mcg dose. (see DOSAGE AND ADMINISTRATION).

When dispensing, do not substitute ABSTRAL prescription from any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of ABSTRAL compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ABSTRAL for any other fentanyl product may result in fatal overdose. ABSTRAL is NOT a generic version of any other fentanyl product.

The concomitant use of ABSTRAL with strong and moderate cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression (see **DRUG INTERACTIONS**).

Patients and their caregivers must be instructed that ABSTRAL contains a medicine in an amount which can be fatal to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All packs must be kept out of reach of children and opened packs properly discarded.

General

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

It is important that the long-acting opioid treatment used to treat the patient's persistent pain has been stabilized before starting Abstral therapy. In cases where patients regularly experience more than 4 breakthrough pain episodes per day, increasing the opioid maintenance dose has to be considered before starting the titration process.

Cardiovascular

Intravenous fentanyl may produce bradycardia. Therefore, ABSTRAL should be used with caution in patients with bradyarrhythmias.

Concomitant Use of Central Nervous System Depressants

The concomitant use of ABSTRAL with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may increase depressant effects (e.g., hypoventilation, hypotension, and profound sedation.

Patients on concomitant CNS depressants must be monitored for a change in opioid effects that may warrant an adjustment to the dose of Abstral (see **DRUG INTERACTIONS**).

Concomitant Use of CYP 3A4 Inhibitors

Fentanyl is metabolized by the CYP 3A4 isoenzyme in the liver and intestinal mucosa. Hence caution is advised if fentanyl is given concomitantly with CYP 3A4 inhibitors. Inhibitors of CYP 3A4 such as macrolide antibiotics (e.g. erythromycin, clarithromycin, telithromycin), azole antifungals (e.g. ketoconazole, itraconazole, and fluconazole) and certain protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir) as well as the calcium channel blocker verapamil, the anti-emetic aprepitant, and the antidepressant nefazodone may increase the bioavailability of swallowed fentanyl and may also decrease its systemic clearance resulting in increased or prolonged opioid effects which may cause potentially fatal respiratory depression.

Similar effects could be seen after concurrent ingestion of grapefruit juice, which is known to inhibit CYP 3A4. Patients receiving Abstral who begin therapy with, or increase the dose of, CYP 3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time (see **DRUG INTERACTIONS**).

Dependence/Tolerance

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. However, iatrogenic addiction following therapeutic use of opioids is rare.

Guide the administration of Abstral by the response of the patient. Physical dependence is not ordinarily a concern when treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).
Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

Potential for Abuse and Diversion

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers. "Drug seeking" behaviour includes emergency calls or visits near the end of office hours; refusal to undergo appropriate examination, testing or referral; repeated "loss" of prescriptions; tampering with prescriptions; "doctor shopping" to obtain additional prescriptions; and reluctance to provide prior medical records or contact information for other treating physician(s).

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since ABSTRAL may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper patient assessment, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Drug or Alcohol Dependence
Use of Abstral in combination with CNS depressants, including alcohol, can result in increased risk to the patient (see **DRUG INTERACTIONS** section).

Head Injuries and Increased Intracranial Pressure

ABSTRAL should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

Hepatic/Biliary/Pancreatic

ABSTRAL should be administered with caution to patients with liver dysfunction.

The influence of liver impairment on the pharmacokinetics of ABSTRAL has not been determined. However, the clearance of intravenously administered fentanyl is decreased in hepatic disease due to alterations in metabolic clearance and plasma proteins.

Fentanyl may cause spasm of the sphincter of Oddi and ABSTRAL should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in serum amylase concentration.

Concomitant Use of MAO Inhibitors

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

Psychomotor Impairment

Opioid analgesics like fentanyl may impair the mental or physical ability required for the performance of potentially dangerous tasks. Patients should not drive or operate machinery if they are feeling sleepy or dizzy, have blurred or double vision, or have difficulty in concentrating while using Abstral.

Renal

The influence of renal impairment on the pharmacokinetics of Abstral has not been determined. However, the clearance of intravenously administered fentanyl is decreased in renal disease due to alterations in metabolic clearance and plasma proteins.

Respiratory

Respiratory Depression (Hypoventilation)

Respiratory depression is the chief hazard of opioids, including fentanyl, the active ingredient in Abstral. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of Abstral. Particular caution should be used when titrating Abstral in patients with non-severe chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression, as even doses of Abstral that are normally therapeutic may further decrease respiratory drive to the point of respiratory failure.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Use in Patients with Chronic Pulmonary Disease

Fentanyl should be used with caution in patients with chronic pulmonary disease, patients with decreased respiratory reserve and others with potentially compromised respiration, including obstructive long condition. Normal analgesic doses of opioids may further decrease respiratory

drive in these patients to the point of respiratory failure.

Special Populations

Pregnant Women

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 anomalies 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, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl has been shown to impair fertility and to have an embryocidal effect in rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for ABSTRAL.

Fentanyl citrate was not teratogenic when administered to pregnant animals. In published studies, pregnant rats were treated with fentanyl (10, 100, or 500 mcg/kg/day) via implanted micro-osmotic minipumps from Day 7 to 21 of their 21-day gestation period. The highest dose in these tests, 500 mcg/kg/day was approximately 6 times the human dose of 800 mcg every 6 hours on a mg/m^2 basis. Intravenous administration of fentanyl (10 or 30 mcg/kg/day) to pregnant female rats from gestation Day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

Labor and Delivery

Fentanyl passes through the placenta and may cause respiratory depression in the fetus. The placental transfer ratio is 0.44 (fetal:maternal ratio 1.00:2.27). ABSTRAL is not indicated during delivery.

Nursing Women

Fentanyl passes into breast milk; therefore, women should not breast-feed while taking ABSTRAL because of the possibility of sedation and respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using ABSTRAL.

Pediatrics (< 18 years of age)

Abstral is not indicated in children under the age of 18 years, as dosage requirements for the safe and effective use of ABSTRAL have not been established for this patient population.

Geriatrics (>65 years of age)

Elderly patients may be more sensitive to the effects of fentanyl compared with the younger population. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects. Therefore, exercise caution when titrating Abstral in elderly patients.

Information for patients/caregiver

The physician should advise the patient/caregiver that a Consumer Information leaflet is included in the package of ABSTRAL dispensed to the patient. The patient/caregiver should read this leaflet very carefully before starting treatment with ABSTRAL.

Patients receiving ABSTRAL or their caregiver should be given the following instructions by the physician:

1. Patients should be informed that accidental use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.

2. Patients should be advised that ABSTRAL contains fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone and oxymorphone.

3. Patients should be advised that ABSTRAL should be taken as directed by the physician and the dose of ABSTRAL should NEVER be adjusted without the prescribing physician's instruction.

    a. The dose of ABSTRAL will be adjusted until the physician finds the right dose for the patient that achieves adequate analgesia with tolerable side effects.
    b. ABSTRAL should be used only one time for each episode of breakthrough cancer pain. Doses of Abstral should be separated by at least 2 hours.
    c. ABSTRAL should not be used for more than four episodes of breakthrough cancer pain in one day. If the patient has more than four episodes of breakthrough pain each day, the dose of the opioid pain medicine for the persistent baseline cancer pain may need to be changed.
    d. Once the right dose for the patient has been found, the patient should not change the dose of ABSTRAL unless directed by their physician.

4. ABSTRAL comes in individually sealed child-resistant blister packages. Patients should be advised not to open the package until ready to use. Once opened, the entire

ABSTRAL sublingual tablet should be used right away. Instructions for opening the blister package are included in the Consumer Information.

5. Patients should be advised not to eat or drink anything until the ABSTRAL sublingual tablet is completely dissolved under their tongue and they can no longer feel it in their mouth.

6. Patients should be advised to never chew, suck or swallow this medication, as this will decrease its activity.

7. Patients should be advised that Abstral may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).

8. Patients should be advised that ABSTRAL should not be combined with alcohol or other CNS depressants (e.g. sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

9. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with ABSTRAL.

10. Patients should be advised that ABSTRAL contains fentanyl, a drug with high potential for abuse. Patients, family members and caregivers should be advised to protect ABSTRAL from theft or misuse in the work or home environment.

11. Patients should be instructed to keep ABSTRAL in a secure place out of the reach of children due to the high risk of **fatal respiratory depression**.

12. When ABSTRAL is no longer needed, the unused ABSTRAL sublingual tablets should be removed from their blister units and dropped into the toilet. The toilet should be flushed after all tablets are dropped in it. Blister packages and cartons should not be dropped in the toilet. ABSTRAL rapidly and completely disintegrates on administration. If for any reason a tablet is removed from the mouth before it has completely disintegrated, it should be disposed of in accordance with the instructions provided above.

13. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.

14. Patients should be advised to report episodes of uncontrolled breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

15. Patients should be advised of the most common adverse reactions that may occur while taking ABSTRAL: nausea, constipation, somnolence and headache.

16. Patients should be advised that ABSTRAL should never be given to anyone other than the individual for whom it was prescribed.

17. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with ABSTRAL. Women who are breast-feeding or pregnant should not use ABSTRAL**.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly observed adverse reactions with ABSTRAL (fentanyl citrate sublingual tablet) include typical opioid side effects, such as nausea, constipation, somnolence and headache. Opioid side effects should be expected and managed accordingly.

The most serious adverse reactions associated with all opioids including ABSTRAL are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. **Follow all patients for symptoms of respiratory depression**.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of ABSTRAL has been evaluated in 311 opioid-tolerant adult cancer patients with breakthrough pain. Two hundred and seventy (270) of these patients were treated in multiple dose Phase III studies. The average duration of therapy for patients in multiple dose studies was 131 days with 120 treated for ≥ 60 days, 110 treated for ≥ 90 days, and 44 patients completed the studies after 1 year.

During the course of the multiple-dose studies in cancer patients, substantial numbers of patients were exposed to more than 100 doses of ABSTRAL; 36 subjects in the 800 mcg assigned dose group took more than 500 doses of ABSTRAL.

Common Clinical Trial Adverse Drug Reactions (≥ 5%)

Table 1 lists the treatment-emergent adverse events, regardless of causality, with a frequency of ≥ 5% that occurred in any of the doses during short-term administration during titration periods of multiple-dose Phase III studies and are listed by maximum dose received.

In short-term administration, the most common ADR was nausea in 8.9% and somnolence in 5.2 % of subjects.

Table 1 Summary of TEAEs Reported During the Open-label Titration Phase in at Least 5% of Patients in Any Dose Group – Multiple-dose Studies in Cancer Patients

System Organ Class Preferred Term	Abstral Dose						Total (N=270) n (%)
	100 mcg (N=22) n (%)	200 mcg (N=23) n (%)	300 mcg (N=55) n (%)	400 mcg (N=38) n (%)	600 mcg (N=52) n (%)	800 mcg (N=80) n (%)	
Gastrointestinal disorders							
Nausea	1 (4.5)	4 (17.4)	9 (16.4)	2 (5.3)	2 (3.8)	6 (7.5)	24 (8.9)
Vomiting	1 (4.5)	2 (8.7)	2 (3.6)	1 (2.6)	1 (1.9)	3 (3.8)	10 (3.7)
Diarrhea	0	2 (8.7)	3 (5.5)	0	2 (3.8)	0	7 (2.6)
Nervous system disorders							
Somnolence	0	2 (8.7)	4 (7.3)	4 (10.5)	2 (3.8)	2 (2.5)	14 (5.2)
Dizziness	1 (4.5)	1 (4.3)	3 (5.5)	4 (10.5)	0	1 (1.3)	10 (3.7)
Headache	0	0	1 (1.8)	1 (2.6)	3 (5.8)	1 (1.3)	6 (2.2)
General disorders and administration site conditions							
Fatigue	1 (4.5)	2 (8.7)	2 (3.6)	0	2 (3.8)	1 (1.3)	8 (3.0)
Asthenia	0	1 (4.3)	0	2 (5.3)	0	0	3 (1.1)
Psychiatric disorders							
Insomnia	1 (4.5)	2 (8.7)	0	1 (2.6)	2 (3.8)	0	6 (2.2)
Anxiety	2 (9.1)	1 (4.3)	0	0	0	0	3 (1.1)
Blood and lymphatic system disorders							
Anemia	0	0	3 (5.5)	1 (2.6)	0	0	4 (1.5)

Table 2 lists treatment-emergent adverse events, regardless of causality, with an overall frequency of ≥5% that occurred during the open-label maintenance phase of multiple-dose Phase III studies and are listed by dose received.

During the open-label maintenance phase, a total of 28 TEAEs were reported by at least 5% of patients overall. Of these 28 TEAEs, nausea (22.0% of patients), vomiting (13.7%); fatigue (12.5%), edema peripheral (10.7%), and stomatitis, back pain, and dehydration (10.1% each) occurred at the highest incidences.

Table 2. Summary of TEAEs Reported During the Open-label Maintenance Phase in at Least 5% of Patients Overall by Dose – Multiple-dose Studies in Cancer Patients

System Organ Class Preferred Term	Abstral Dose						Total
	100 mcg (N=7) n (%)	200 mcg (N=12) n (%)	300 mcg (N=22) n (%)	400 mcg (N=20) n (%)	600 mcg (N=35) n (%)	800 mcg (N=72) n (%)	(N=168) n (%)
Gastrointestinal disorders							
Nausea	3 (42.9)	1 (8.3)	6 (27.3)	2 (10.0)	6 (17.1)	19 (26.4)	37 (22.0)
Vomiting	0	0	4 (18.2)	4 (20.0)	6 (17.1)	9 (12.5)	23 (13.7)
Stomatitis	1 (14.3)	1 (8.3)	2 (9.1)	3 (15.0)	4 (11.4)	6 (8.3)	17 (10.1)
Constipation	0	0	2 (9.1)	3 (15.0)	2 (5.7)	7 (9.7)	14 (8.3)
Diarrhea	0	0	2 (9.1)	3 (15.0)	5 (14.3)	3 (4.2)	13 (7.7)
Abdominal pain	0	1 (8.3)	1 (4.5)	1 (5.0)	3 (8.6)	4 (5.6)	10 (6.0)
Infections and infestations							
Bronchitis	1 (14.3)	0	1 (4.5)	2 (10.0)	0	6 (8.3)	10 (6.0)
Upper respiratory tract infection	0	0	0	0	7 (20.0)	3 (4.2)	10 (6.0)
Pneumonia	1 (14.3)	0	1 (4.5)	1 (5.0)	1 (2.9)	5 (6.9)	9 (5.4)
Urinary tract infection	0	1 (8.3)	1 (4.5)	0	4 (11.4)	3 (4.2)	9 (5.4)
General disorders and administration site conditions							
Fatigue	0	0	3 (13.6)	3 (15.0)	6 (17.1)	9 (12.5)	21 (12.5)
Edema peripheral	2 (28.6)	1 (8.3)	1 (4.5)	2 (10.0)	4 (11.4)	8 (11.1)	18 (10.7)
Asthenia	0	1 (8.3)	1 (4.5)	1 (5.0)	5 (14.3)	6 (8.3)	14 (8.3)
Nervous system disorders							
Headache	0	1 (8.3)	1 (4.5)	2 (10.0)	1 (2.9)	7 (9.7)	12 (7.1)
Muscoloskeletal and connective tissue disorders							
Back pain	1 (14.3)	2 (16.7)	2 (9.1)	0	4 (11.4)	8 (11.1)	17 (10.1)
Arthralgia	1 (14.3)	0	1 (4.5)	3 (15.0)	3 (8.6)	6 (8.3)	14 (8.3)
Pain in extremity	2 (28.6)	0	2 (9.1)	2 (10.0)	0	4 (5.6)	10 (6.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Cancer pain	1 (14.3)	0	0	1 (5.0)	4 (11.4)	8 (11.1)	14 (8.3)
Investigations							

System Organ Class Preferred Term	Abstral Dose						Total (N=168) n (%)
	100 mcg (N=7) n (%)	200 mcg (N=12) n (%)	300 mcg (N=22) n (%)	400 mcg (N=20) n (%)	600 mcg (N=35) n (%)	800 mcg (N=72) n (%)	
Weight decreased	0	1 (8.3)	0	7 (35.0)	2 (5.7)	5 (6.9)	15 (8.9)
Respiratory, thoracic and mediastenal disorders							
Dyspnea	0	1 (8.3)	0	2 (10.0)	5 (14.3)	2 (2.8)	10 (6.0)
Metabolism and nutrition disorders							
Dehydration	0	1 (8.3)	1 (4.5)	3 (15.0)	3 (8.6)	9 (12.5)	17 (10.1)
Anorexia	0	0	0	3 (15.0)	4 (11.4)	6 (8.3)	13 (7.7)
Hypokaleamia	0	0	2 (9.1)	1 (5.0)	1 (2.9)	6 (8.3)	10 (6.0)
Skin and subcutaneous tissue disorders							
Rash	0	1 (8.3)	0	1 (5.0)	3 (8.6)	5 (6.9)	10 (6.0)
Blood and lymphatic system disorders							
Anemia	0	2 (16.7)	1 (4.5)	2 (10.0)	6 (17.1)	5 (6.9)	16 (9.5)
Psychiatric disorders							
Insomnia	1 (14.3)	0	0	0	3 (8.6)	9 (12.5)	13 (7.7)
Anxiety	1 (14.3)	1 (8.3)	0	1 (5.0)	3 (8.6)	6 (8.3)	12 (7.1)
Vascular disorders							
Hypotension	0	1 (8.3)	1 (4.5)	0	3 (8.6)	4 (5.6)	9 (5.4)

Less Common Clinical Trial Adverse Drug Reactions (<5%)

The following adverse events were reported in the administration of Abstral at a frequency <5% in the safety and efficacy studies (two Phase III studies).

Blood and lymphatic system disorders: coagulopathy, febrile neutropenia, iron deficiency anemia, leucopenia, leukocytosis, lymphadenopathy, neutropenia, pancytopenia, thrombocytopenia.

Cardiac disorders: bradycardia, sinus bradycardia, sinus tachycardia, tachycardia, ventricular tachycardia.

Ear and labyrinth disorders: ear pain, vertigo.

Eye disorders: vision blurred.

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal pain upper, aphthous stomatitis, ascites, cheilitis, colonic polyp, dental caries, dry mouth, dyspepsia, dysphagia, epigastric discomfort, fecal incontinence, gastritis, gastroesophageal reflux disease, gingival ulceration, gingivitis, hemorrhoids, hyperchlorhydria, impaired gastric emptying, intestinal obstruction, lip ulceration, mouth ulceration, small intestinal obstruction, stomach discomfort, tongue disorder, tongue ulceration, toothache.

General disorders and administration site conditions: axillary pain, chills, drug withdrawal syndrome, facial pain, gait disturbance, generalized edema, malaise, mucosal inflammation, non-cardiac chest pain, pain, pitting edema, pyrexia.

Hepatobiliary disorders: cholecystitis, hepatomegaly, jaundice.

Immune system disorders: drug hypersensitivity.

Infections and infestations: candidiasis, cellulitis, central line infection, cystitis, gastroenteritis viral, herpes zoster, hordeolum, infection, influenza, lobar pneumonia, lower respiratory tract infection, lung infection, nasopharyngitis, oropharyngeal candidiasis, pharyngitis, pharyngitis streptococcal, respiratory tract infection, sinusitis, tooth abscess, tooth infection.

Injury, poisoning and procedural complications: accidental overdose, contusion, excoriation, fall, procedural nausea, procedural pain, rib fracture, skin laceration, thermal burn, tooth fracture.

Investigations: blood alkaline phosphatase increased, blood creatinine increased, blood potassium decreased, blood potassium increased, blood testosterone decreased, blood urea increased, blood uric acid increased, breath sounds abnormal, cardiac murmur, liver function test abnormal, weight increased.

Metabolism and nutrition disorders: cachexia, decreased appetite, hypoglycaemia, hypomagnesaemia, hyponatraemia.

Musculoskeletal and connective tissue disorders: exostosis, groin pain, intervertebral disc protrusion, joint stiffness, joint swelling, muscle spasms, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, pain in jaw.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): breast cancer metastatic, colon cancer metastatic, fibroadenoma of breast, lung cancer metastatic, lung neoplasm, metastases to central nervous system, metastases to liver, metastatic pain, prostate cancer metastatic.

Nervous system disorders: amnesia, convulsion, coordination abnormal, disturbance in attention, dizziness, dysgeusia, hypoaesthesia, lethargy, migraine, neuropathy peripheral, paraesthesia, parosmia, sensory loss, somnolence, spinal cord compression, tremor.

Psychiatric disorders: affect lability, agitation, confusional state, depression, disorientation, dysphoria, euphoric mood, mental status change, panic attack, paranoia, sleep disorder, stress.

Renal and urinary disorders: dysuria, nephrolithiasis, pollakiuria, renal acute failure, urinary incontinence, urinary retention.

Reproductive system and breast disorders: erectile dysfunction, pelvic pain, vaginal hemorrhage.

Respiratory, thoracic and mediastinal disorders: atelectasis, chronic obstructive pulmonary disease, cough, epistaxis, hypoxia, nasal congestion, oropharyngeal pain, pleural effusion, pulmonary embolism, pulmonary oedema, respiratory failure, respiratory tract congestion, throat tightness, wheezing.

Skin and subcutaneous tissue disorders: alopecia, decubitus ulcer, dermatitis, drug eruption, ecchymosis, erythema, hyperhidrosis, increased tendency to bruise, night sweats, pruritus, pruritus allergic, skin lesion, skin ulcer, swelling face.

Vascular disorders: deep vein thrombosis, hypertension, hot flush, lymphoedema, orthostatic hypotension, pallor.

Post-Market Adverse Drug Reactions

Spontaneous reports received are consistent with the safety profile observed in clinical trials.

Post-marketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome following the concomitant use of fentanyl with a serotonergic drug, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor (See also **DRUG INTERACTIONS**).

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Additive Effects of Other CNS Depressants

The concomitant use of ABSTRAL (fentanyl citrate sublingual tablet) with other CNS depressants, other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may increase depressant effects (e.g., hypoventilation, hypotension, and profound sedation).

Patients on concomitant CNS depressants must be monitored for a change in opioid effects that may warrant adjustment to the dose of Abstral.

Drug or Alcohol Dependence

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.

CYP 3A4 Inhibitors

Fentanyl is rapidly and extensively metabolized mainly by the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore, potential interactions may occur when ABSTRAL is given concurrently with agents that affect CYP3A4 activity. The concomitant use of Abstral with CYP 3A4 **inhibitors** (e.g. indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving Abstral who begin therapy with, or increase the dose of, CYP 3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases of both Abstral and CYP 3A4 inhibitors should be done conservatively (see **WARNINGS AND PRECAUTIONS** section).

The concomitant use of Abstral with CYP 3A4 **inducers** (e.g. barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of Abstral (see **WARNINGS AND PRECAUTIONS** section).

MAO Inhibitors

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

Serotonergic Drugs

Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life threatening condition. (See also **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Drug-Food Interactions

Grapefruit and grapefruit juice, which are CYP3A4 inhibitors, may result in a potentially dangerous increase in fentanyl plasma concentrations.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyle products have not been established.

DOSAGE AND ADMINISTRATION

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use (see **Serious Warnings and Precautions Box**).

ABSTRAL (fentanyl citrate sublingual tablet) should only be prescribed by persons knowledgeable in the management of patients receiving potent opioids for the treatment of pain.

Dosing Considerations

ABSTRAL is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least: 60 mg morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg of oxycodone daily, 8 mg oral hydromorphone daily, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer.

ABSTRAL doses must be individualized based upon the status of each patient and should be assessed at regular intervals. Individually titrate ABSTRAL to a dose that provides adequate analgesia with an acceptable level of adverse reactions.

Recommended Dose and Dosage Adjustment

Dose Titration

The dose of ABSTRAL is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and **MUST** be determined by dose titration. The optimal dose of ABSTRAL will be determined by dose titration in individual patients.

Several dose strengths of ABSTRAL are available for use during the dose titration phase.

Starting Dose

All patients MUST begin treatment using one 100 mcg ABSTRAL sublingual tablet.

Patients should be carefully supervised until an optimal dose is reached for breakthrough pain control, i.e. which provides adequate analgesia with acceptable adverse reactions for each episode of breakthrough pain.

Direct switching from other fentanyl containing products to ABSTRAL must not occur without re-titration because of differences in pharmacokinetic properties, different absorption profiles and individual variability. If patients are switched from another fentanyl containing product, a new dose titration with ABSTRAL is required and patients must be started on **no greater than 100 mcg of ABSTRAL**.

When prescribing, do not switch patients from any other fentanyl product to Abstral as Abstral is not equivalent on a mcg per mcg basis with any other fentanyl product.

Start all patients with a single 100 mcg tablet.

- If adequate analgesia is obtained within 30 minutes of administration of the 100 mcg tablet, continue to treat subsequent episodes of breakthrough pain with this dose.
- Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.

Subsequent Dose/Titration

The following dose titration regimen is recommended, however in all cases the physician should take into account the clinical need of the individual patient, age, co-existing illness or medical condition, and concomitant medications.

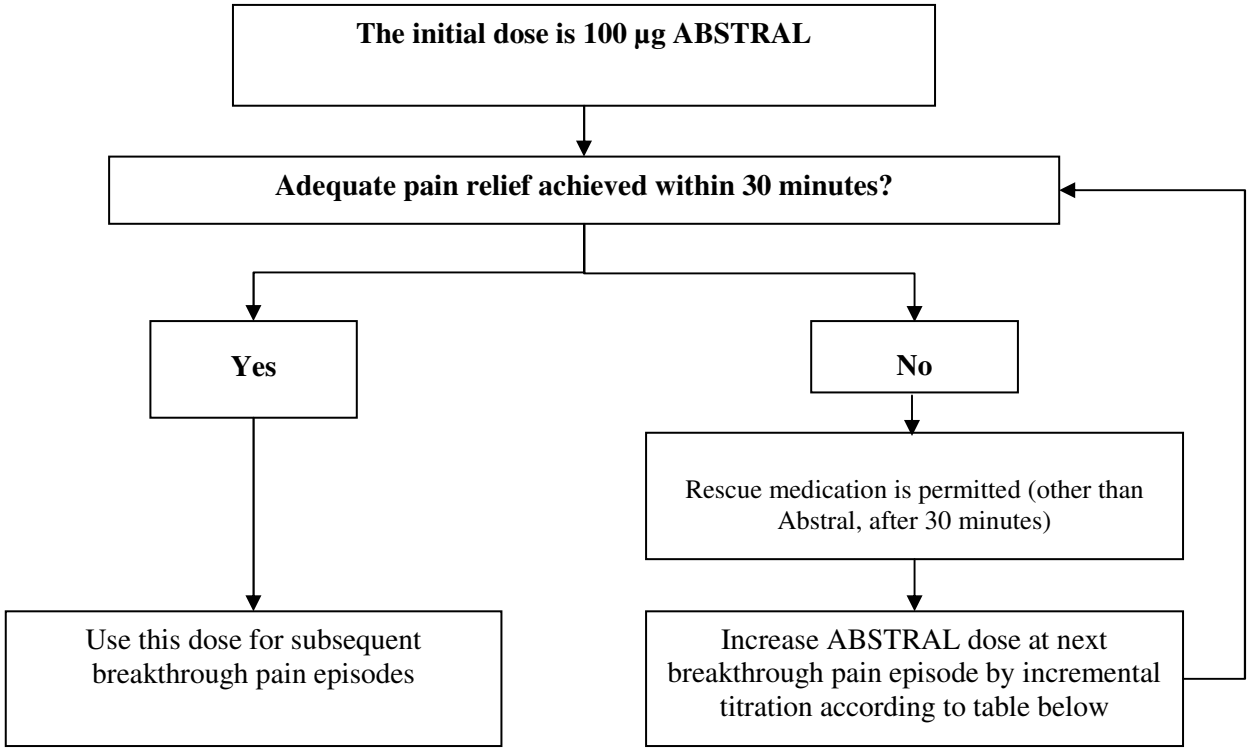
If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Increase the dose by 100 mcg multiples up to 400 mcg as needed. If adequate analgesia is not obtained with a 400 mcg dose, the next titration step is 600 mcg. If adequate analgesia is not obtained with a 600 mcg dose, the next titration step is 800 mcg. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time. **Doses above 800 mcg Abstral should not be used.**

Once adequate pain relief *is achieved* with a dose between 100 and 800 mcg Abstral, the patient should get a prescription for Abstral of the dose determined by titration (i.e., 100, 200, 300, 400, 600 or 800 mcg) to treat subsequent episodes.

Single doses should be separated by at least 2 hours. Abstral should only be used once per breakthrough cancer pain episode, i.e. Abstral should not be redosed within an episode.

During any episode of breakthrough cancer pain, if adequate pain relief *is not achieved* after Abstral, the patient may use a rescue medication (other than Abstral, after 30 minutes) as directed by their healthcare provider.

ABSTRAL Titration Process



ABSTRAL dosing for a subsequent episode should be separated by at least 2 hours

ABSTRAL dose	Using
200 mcg	2 x 100 mcg tablets, *or* 1 x 200 mcg tablets
300 mcg	3 x 100 mcg tablets, *or* 1 x 300 mcg tablets
400 mcg	4 x 100 mcg tablets, *or* 2 x 200 mcg tablets, *or* 1 x 400 mcg tablets
600 mcg	3 x 200 mcg tablets, *or* 1 x 600 mcg tablets
800 mcg	4 x 200 mcg tablets, *or* 1 x 800 mcg tablets

In order to minimize the risk of opioid-related adverse reactions and to identify the appropriate dose, it is imperative that patients be supervised closely by health professionals during the titration process.

Maintenance Therapy

Once an appropriate dose for pain management has been established, instruct patients to use only one ABSTRAL tablet of the appropriate strength per dose. Maintain patients on this dose.

If adequate analgesia is not obtained after use of ABSTRAL, the patient may use rescue medication other than Abstral (after 30 minutes) as directed by their health care provider. No more than one dose of ABSTRAL may be used to treat an episode of breakthrough pain. Patients must wait at least 2 hours before treating another episode of breakthrough 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.

During maintenance treatment, if the prescribed dose no longer adequately manages the breakthrough cancer pain episode for several consecutive episodes, increase the dose of Abstral as described in Dose Titration. Once a successful dose is determined, each episode is treated with a single tablet. Use of Abstral should be limited to four episodes of breakthrough pain per day, and administration of Abstral must be separated by at least 2 hours.

If more than four episodes of breakthrough pain are experienced per day, then the dose of the long-acting opioid used for persistent underlying cancer pain should be re-evaluated. If the long-acting opioid or dose of long-acting opioid is changed, then 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 opiate analgesic is monitored carefully by a health professional.

Discontinuation of Therapy

For patients no longer requiring opioid therapy, the ABSTRAL dose should be taken into consideration before a gradual downward titration of other opioids to minimize possible withdrawal effects such as anxiety, tremor, sweating, paleness, nausea and vomiting.

In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, ABSTRAL therapy can usually be discontinued immediately.

Use in children

ABSTRAL is not indicated in children under the age of 18 years, as dosage requirements for the safe and effective use of ABSTRAL have not been established for this patient population.

Use in the elderly

Elderly patients may be more sensitive to the effects of fentanyl, compared with the younger population. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects. Therefore, exercise caution when titrating ABSTRAL in elderly patients.

Use in special patient populations

Special care should be taken during the titration process in patients with kidney or liver dysfunction.

Administration of ABSTRAL

ABSTRAL tablets should be placed on the floor of the mouth directly under the tongue immediately after removal from the blister unit. ABSTRAL tablets should not be chewed, sucked or swallowed, but allowed to completely dissolve in the sublingual cavity. Patients should be advised not to eat or drink anything until the tablet is completely dissolved.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Clinical Presentation

The manifestations of ABSTRAL (fentanyl citrate sublingual tablet) overdosage are an extension of its pharmacological actions with the most serious significant effect being respiratory depression.

Immediate Management of Opioid Overdose

Immediate management of opioid overdose includes removal of the ABSTRAL tablet, if still in the mouth. Ensure a patent airway, physical and verbal stimulation of the patient, assessment of the level of consciousness, ventilatory and circulatory status, and assisted ventilation (ventilatory support) if necessary.

Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

For treatment of accidental ingestion *in the opioid non-tolerant person,* provide ventilatory support, obtain intravenous access, and administer naloxone or other opioid antagonists as

clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration of naloxone or other opioid antagonists may be necessary. Consult the product monograph of the individual opioid antagonist for details about such use.

Treatment of Overdose in Opioid-Tolerant Patients

For treatment of overdose in *opioid-tolerant patients*, provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

Although muscle rigidity interfering with respiration has not been seen following the use of ABSTRAL, this is possible with fentanyl and other opioids. If it occurs, it should be managed by the use of assisted ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

General Considerations for Overdose

Management of severe ABSTRAL overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and gastrointestinal decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of ABSTRAL, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by the administration of an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fentanyl, a pure opioid agonist, acts primarily through interaction with μ-opioid receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The clinically most useful pharmacological effect of the interaction of fentanyl with μ-opioid receptors is analgesia.

Pharmacodynamics

Fentanyl is a potent μ-opioid agonist / 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 gastro-intestinal function are typical of opioid analgesics and are considered to be class effects.

Pharmacological effects of opioid agonists include analgesia, anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis and cough suppression. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by tolerability of side effects, the more serious of which may include somnolence and respiratory depression.

Secondary actions include increase in the tone and decrease in the contractions of the gastrointestinal smooth muscle, which results in prolongation of gastrointestinal transit time and may be responsible for the constipation typically seen with opioids.

Analgesia

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3-to-5-minute half-life). In opioid-naive individuals, analgesia occurs at blood levels of 1 to 2 ng/mL, while blood levels of 10-20 ng/mL would produce surgical anaesthesia and profound respiratory depression.

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of ABSTRAL (fentanyl citrate sublingual tablet) should be individually titrated to achieve the desired effect.

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a μ-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-

like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g. pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Urinary and Gastrointestinal Systems

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain. Other opioid induced-effects may include a reduction in gastric, biliary, and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

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.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species (rats, dogs). Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System

All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with sublingual fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration.

Therefore, physicians and other healthcare providers should be aware of this potential complication.

Pharmacokinetics

Absorption:

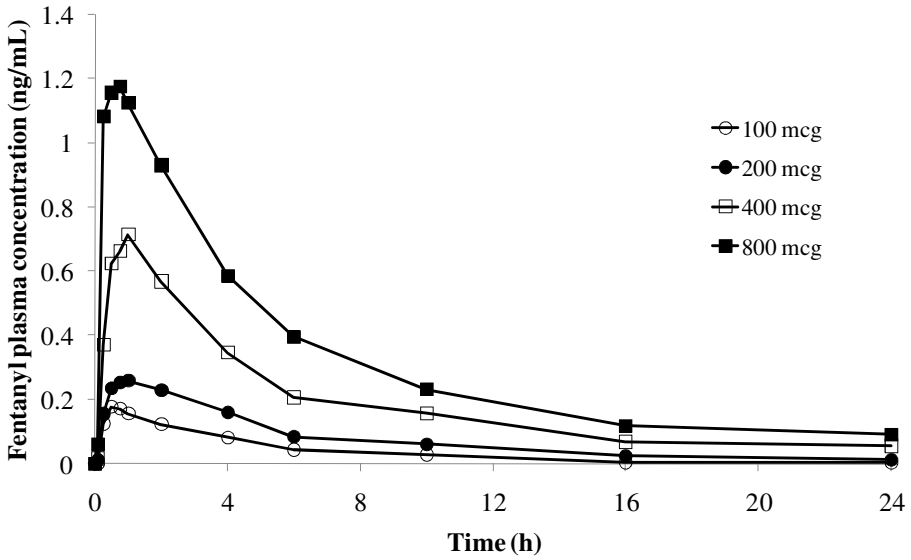
Fentanyl is a highly lipophilic drug. It is absorbed very rapidly through the oral mucosa and more slowly through the gastrointestinal tract. Orally administered fentanyl undergoes pronounced hepatic and intestinal first pass effects.

ABSTRAL (fentanyl citrate sublingual tablet) is a rapidly disintegrating sublingual tablet formulation. Its absorption across the mucosa avoids first-pass metabolism, resulting in a substantially greater bioavailability than after oral administration. Rapid absorption of fentanyl occurs over about 30 minutes following administration of ABSTRAL.

The bioavailability of ABSTRAL has been estimated to be 54%.

Dose proportionality across the 100-800 microgram ABSTRAL dose range has been demonstrated after single and repeated dosing in a parallel-group Phase I study (n=12 for each dose). Mean plasma fentanyl levels following single doses of ABSTRAL are shown in Figure 1.

Figure 1: Mean Plasma Fentanyl Concentration Versus Time After Administration of Single Doses of 100, 200, 400 and 800 mcg ABSTRAL to Healthy Subjects



Pharmacokinetic parameters are presented in Table 3.

Table 3. Mean (CV%) Fentanyl Pharmacokinetic Parameters After Administration of 100, 200, 400 and 800 µg Doses of ABSTRAL to Healthy Subjects (n=12 per Dose Level)

Parameter	Unit	Abstral ODT dose			
		100 µg	200 µg	400 µg	800 µg
C_{max}	(ng/mL)	0.187 (33)	0.302 (31)	0.765 (38)	1.42 (33)
T_{max} [a]	(min)	30 [19-120]	52 [16-240]	60 [30-120]	30 [15-60]
T_{first} [a]	(min)	15 [14-25]	15 [6-16]	15 [5-15]	5 [5-15]
AUC_{0-inf}	(ng.h/mL)	0.974 (34)	1.92 (27)	5.49 (35)	8.95 (33)
$T_{1/2}$	(h)	5.02 (51)	6.67 (30)	13.5 (37)	10.1 (34)

a: median (range)

Overall, the range of individual t_{max} and t_{first} values was similar for the tested dose level. Individual dose-normalized C_{max} and AUC values were within the same range for all dose levels, indicating dose proportionality across the tested dose range of 100 to 800 µg. Dose proportionality was also shown statistically after single and multiple dosing.

Similar pharmacokinetic profiles were seen in cancer patients.

Distribution: Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the liver, brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 72-84% in humans. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The average volume of distribution for fentanyl is 3-5 L/kg.

Metabolism: The absorption of fentanyl following administration of Abstral occurs mainly through the oral mucosa, minimizing hepatic and intestinal first pass effect. Fentanyl is metabolised in the liver by *N*-dealkylation and hydroxylation via the cytochrome p450 isoenzyme CYP3A4 to compounds that were not found to be pharmacologically active in animal studies**.**

Excretion: Fentanyl is predominantly eliminated as metabolites in urine and to a lesser extent in faeces. After an intravenous dose, less than 8% of the total dose is eliminated unchanged. Approximately 75% of an intravenous dose is excreted in urine and 9% in faeces. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 - 0.7 L/hr/kg).

Special Populations and Conditions

Pediatrics: The pharmacokinetics of Abstral have not been studied in children and adolescents aged less than 18 years.

Elderly or Debilitated Patients: No formal study has been performed to assess ABSTRAL pharmacokinetics in elderly subjects or patients. In the elderly, elimination of fentanyl may be slower and the terminal elimination half-life may be longer, which may result in accumulation of the active substance and a greater risk of undesirable effects.

Gender: No gender effect was observed in healthy subjects after repeated administration of ABSTRAL.

Race: Fentanyl pharmacokinetics were compared after single ascending doses of 50, 100, 150 and 200 µg ABSTRAL administered to Caucasian (n=11) and Japanese (n=10) healthy male subjects No marked difference was observed between Caucasians and Japanese subjects.

Hepatic insufficiency: The influence of liver impairment on the pharmacokinetics of ABSTRAL has not been determined. However, the clearance of intravenously administered fentanyl is decreased in hepatic disease due to alterations in metabolic clearance and plasma proteins.

Renal insufficiency: The influence of renal impairment on the pharmacokinetics of ABSTRAL has not been determined. However, the clearance of intravenously administered fentanyl is decreased in renal disease due to alterations in metabolic clearance and plasma proteins.

STORAGE AND STABILITY

Storage and handling

Abstral (fentanyl citrate sublingual tablet) is supplied in individual sealed child-resistant blister packages. The amount of fentanyl contained in Abstral can be fatal to a child. The tablet should be used immediately after opening the child-resistant package. Patients and their caregivers must be instructed to keep Abstral out of reach of children.

Store at room temperature between 15°C and 30°C (59-86°F).

Store in the original packaging in order to protect from moisture. Do not use if the blister package has been opened.

SPECIAL HANDLING INSTRUCTIONS

Patients and their caregivers must be instructed that ABSTRAL (fentanyl citrate sublingual tablet) contains medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. Patients and their caregivers must be instructed to keep ABSTRAL out of the reach of children.

Disposal of ABSTRAL

Patients and their household members must be instructed to dispose of any tablets remaining from a prescription as soon as they are no longer needed.

The unused ABSTAL tablet should be removed from its blister init and dropped into the toilet. This should be repeated for each ABSTRAL tablet. Flush the toilet after all unneeded tablets have been put into the toilet. Do not flush the ABSTRAL blister packages or cartons down the toilet.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ABSTRAL (fentanyl citrate sublingual tablet) is formulated as a white tablet available in six strengths, distinguishable by the shape of the tablet.

All tablets are white and show the following distinguishable characteristics:

- 100 µg tablet (fentanyl as fentanyl citrate) is a round tablet
- 200 µg tablet (fentanyl as fentanyl citrate) is an oval-shaped tablet
- 300 µg tablet (fentanyl as fentanyl citrate) is a triangle-shaped tablet
- 400 µg tablet (fentanyl as fentanyl citrate) is a diamond-shaped tablet
- 600 µg tablet (fentanyl as fentanyl citrate) is a “D”-shaped tablet
- 800 µg tablet (fentanyl as fentanyl citrate) is a capsule-shaped tablet

ABSTRAL is supplied in individually sealed child-resistant blister packages contained in a cardboard outer carton, in pack sizes of 10 and or 30 sublingual tablets.

Two pack sizes, of 10 and 30 tablets, are proposed for 100, 200, 300, 400, 600 and 800 mcg strengths.

Blister cards will be packaged in cardboard cartons. The packaging is color-coded for each ABSTRAL tablet strength.

- 100 µg tablet (fentanyl as fentanyl citrate) – LIGHT BLUE
- 200 µg tablet (fentanyl as fentanyl citrate) – DARK ORANGE
- 300 µg tablet (fentanyl as fentanyl citrate) – BROWN
- 400 µg tablet (fentanyl as fentanyl citrate) – VIOLET
- 600 µg tablet (fentanyl as fentanyl citrate) – TURQUOISE
- 800 µg tablet (fentanyl as fentanyl citrate) – INDIGO

The ABSTRAL tablet formulations also contain the following non-medicinal ingredients: mannitol, silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

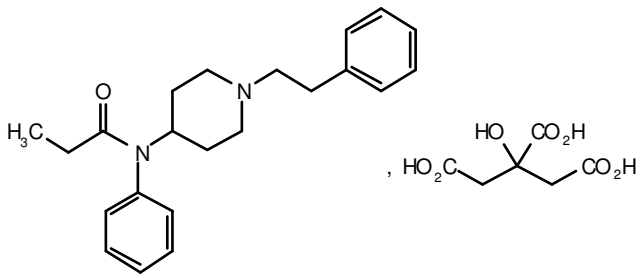
Proper name: Fentanyl citrate

Chemical name: The chemical names of Fentanyl citrate are N-(1-phenethyl-4-piperidyl) propionanilide citrate (1:1) or N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide citrate (1:1)

Molecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Molecular mass: Free base: 336.5
Citrate salt: 528.6

Structural formula:



Physicochemical properties: Fentanyl citrate is a crystalline powder. Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The pKa of the tertiary nitrogens are 7.3 and 8.4. There are no known polymorphs of fentanyl citrate.

Drug Product

ABSTRAL (fentanyl citrate sublingual tablet) is a rapidly disintegrating sublingual tablet formulation containing fentanyl citrate designed for oral transmucosal delivery. The specifications of the finished drug product when tested *in vitro* is to obtain a complete disintegration of the tablet within 30 seconds.

Each available strength of ABSTRAL sublingual tablets contains:

100 micrograms fentanyl (as 157.1 mcg fentanyl citrate),
200 micrograms fentanyl (as 314.2 mcg fentanyl citrate)
300 micrograms fentanyl (as 471.3 mcg fentanyl citrate)
400 micrograms fentanyl (as 628.4 mcg fentanyl citrate)
600 micrograms fentanyl (as 942.6 mcg fentanyl citrate)
800 micrograms fentanyl (as 1257 mcg fentanyl citrate)

CLINICAL TRIALS

The efficacy of Abstral was investigated in Study EN3267-005, a randomized, 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 μg/h; who were on a stable dose of opioid medication for relief of breakthrough pain; and who were experiencing at least one but not more than 4 episodes of breakthrough pain per day.

Patients were titrated to a single effective dose of ABSTRAL for adequate treatment of their breakthrough pain in an initial open-label phase. Patients who were successfully titrated were then included in a double-blind, randomized, placebo-controlled phase of up to 2 weeks, during which 10 episodes of breakthrough 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 pain episodes for up to 12-months.

Open-label titration identified a successful dose of Abstral, within the range of 100 to 800 mcg. A “successful” dose was defined as the one, single dosage strength of ABSTRAL that successfully treated all breakthrough pain episodes that occurred for 2 consecutive days with tolerable side effects. Of the 131 patients enrolled, 53 (40.5%) discontinued during the titration period.

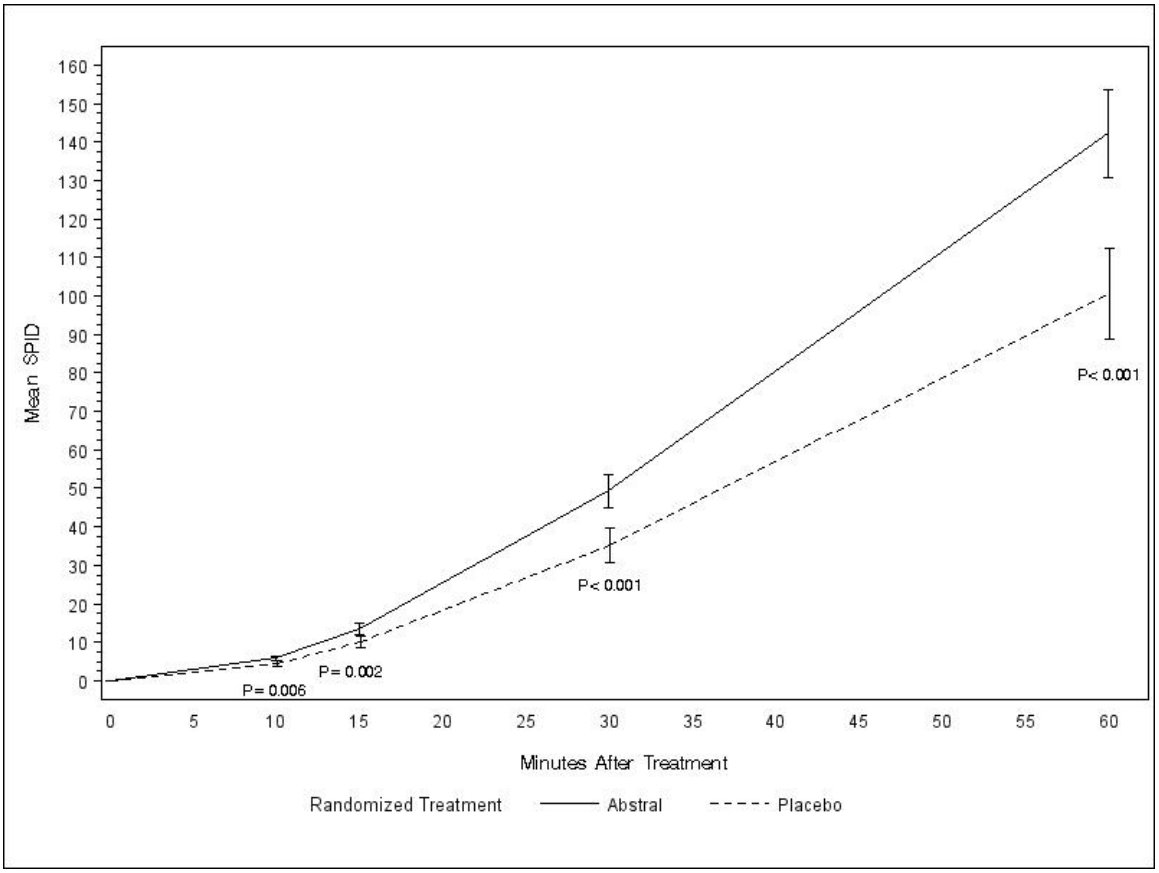
The final titrated dose of ABSTRAL for breakthrough cancer pain was not predictable from the background opioid dose underlying the need for individual titration starting at 100 mcg.

The mean age of subjects in the ITT population (n=131) was 55.0 years (range 21-80 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 pain episodes with study medication. ABSTRAL was found to be superior to placebo in treating cancer breakthrough 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 square means 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 post-dose and the difference continued to be statistically significant through all time points thereafter until the final assessment at 60 minutes post-dose (Figure 2).

Figure 2: Mean Sum Pain Intensity Difference (SPID) for ABSTRAL Compared to Placebo



Secondary endpoints in addition to SPID at time points other than 30 minutes provide supporting evidence of the efficacy of Abstral in breakthrough pain.

ABSTRAL was also shown to provide improved reduction in pain intensity (PID) 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.

The distribution of effective doses identified in the titration phase in this study and in a second Phase III open-label safety study (EN3267-007) following an identical titration regimen is shown in Table 4.

Table 4: Effective dose of ABSTRAL following initial titration in Phase III studies

ABSTRAL Dose (mcg)	n (%) N=174
100	11 (6.3)
200	15 (8.6)
300	35 (20.1)
400	25 (14.4)
600	40 (23.0)
800	48 (27.6)

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

It is well-established that fentanyl is a potent, short-acting, synthetic, pure μ-opioid receptor agonist with the main pharmacologic activity being analgesia. The analgesic potency of fentanyl is approximately 100-fold greater than that of morphine. Fentanyl produces effective analgesia without significant respiratory depression at plasma concentrations ranging from 0.6-2 ng/mL. At higher plasma concentrations (>2 ng/mL), significant respiratory depression may occur. Significant nonrespiratory side effects associated with fentanyl include muscle rigidity, bradycardia, hypotension, nausea and vomiting, pruritus, and urinary retention. As with other narcotic analgesics, subjects may become tolerant to the effects of fentanyl after repeated administration.

Dependence

Recently, the effects of fentanyl withdrawal on brain reward function and somatic withdrawal symptoms were evaluated in male Wistar rats. The rats were trained on a modified discrete-trial intracranial self-stimulation procedure and implanted with 14-day minipumps containing saline or fentanyl citrate (1.2 mg/kg/day). Abrupt cessation of fentanyl administration resulted in a time-dependent elevation in brain reward thresholds and somatic withdrawal signs suggesting a severe deficit in brain reward function. Naloxone resulted in a dose-dependent elevation in brain reward thresholds and somatic withdrawal signs in fentanyl-treated rats; however, it did not alter the response latencies.

Central Nervous System

Behavioural changes observed in rodents and dogs following administration of fentanyl are typical of opioid analgesics (i.e., class effects) In rodents these include increased spontaneous activity, circling, Straub tail, and increased muscle tone. Convulsions occur at high doses that also produce mortality. In dogs, decreased motor activity, ataxia, decreased responsiveness, bradycardia, respiratory depression, salivation and defecation occur. Signs of central depression are reversed immediately by administration of nalorphine.

Cardiovascular Effects

In Vitro Studies
Fentanyl has been tested for activity on cardiac human ether-a-go-go related gene (HERG) K^+ currents. Fentanyl was found to inhibit HERG with an IC_{50} of 1.8 µM. This concentration is approximately 400-fold higher than the concentration reached with the highest strengths of Abstral (approximately 4.4 nM (1.5 µg/mL)).

Fentanyl has also been tested for effects on action potential duration (APD) in canine cardiac purkinje fibers at concentrations of 0.095, 0.19 and 0.95 µM. Fentanyl caused a significant lengthening of action potential duration at all concentrations tested. The effects of fentanyl at 0.19 µM were not reversed by the addition of 5.5 µM naloxone, suggesting that these effects are not mediated by opioid-receptors.

In Vivo Studies
At anaesthetic doses (0.02 mg/kg IV and above), fentanyl produces bradycardia, due at least in part to centrally mediated changes in vagal tone. This effect is preventable or reversible by administration of muscarinic antagonists. In unanesthetized monkeys, no significant effects on cardiovascular function occurred at dose levels below those which produced apnea (0.064 mg/kg).

A study was conducted in dogs to evaluate the effects of intravenously administered fentanyl on cardiovascular and respiratory function. Fentanyl administered at doses of 0.003, 0.01 and 0.03 mg/kg did not affect blood pressure at any dose. There were no effects on heart rate, QT and QTc interval at 0.003 and 0.01 mg/kg. At 0.03 mg/kg, heart rate was statistically significantly decreased at 0.5 hours and 1 hour after dosing; means were 60.8% and 79.0% lower than respective control vales. A small, transient increase in QTc interval from 0.5 to 2 hours after dosing at the same dose level was considered without physiological significance.

Respiratory Effects

All commonly used µ-opioid agonists produce respiratory depression. In animal models, respiratory depression generally occurs rapidly after fentanyl administration and recovers quickly, in parallel with rapid absorption, brain:plasma equilibration and elimination of fentanyl. However, in some cases respiratory depression may be prolonged or even delayed because of tissue redistribution.

In unanaesthetized rhesus monkeys, significant respiratory effects occurred at IV bolus doses of 0.002 mg/kg whereas analgesic effects were identified at double that dose. In dogs, respiratory and analgesic effects occurred at similar cumulative doses. No ceiling effect with regard to respiratory depression was observed in rats or humans.

No effects on the respiratory system were noted in dogs given 0.003 mg/kg fentanyl intravenously. No effects on respiratory rate, PaO_2, or haemoglobin oxygen saturation were observed at any of the administered doses (0.003, 0.01 and 0.03 mg/kg). A decrease in arterial blood pH and an increase in $PaCO_2$ were observed 1 hour after administration at 0.01 and 0.03 mg/kg.

Gastrointestinal Effects

Virtually all commonly used opioids produce GI effects through a combination of central and peripheral actions, which are well described. Gastric and intestinal motility are generally reduced. Prolonged gastric emptying can lead to increased risk of esophageal reflux. Intestinal secretions are decreased, which coupled with delayed passage and increased water absorption, often leads to constipation. It has been reported that transdermal fentanyl produces considerably less intestinal side effects that oral morphine. In rat studies, the safety margin between intestinal effects and efficacy for fentanyl is much higher than that for morphine.

Fentanyl, like other opioids can cause contraction of the smooth muscle along the biliary tree and spasm of the sphincter of Oddi, leading to increased fluid pressure in the gall bladder.

In dogs administered fentanyl by intramuscular injection, no emetic activity was observed at doses of 1 or 2.5 mg/kg, whereas similar doses of morphine produced emesis in 60-90% of animals.

TOXICOLOGY

Single and Repeat Dose Toxicity

Following acute dosing, fentanyl has a high therapeutic index (LD50/ED50); which is higher than for morphine. Clinical signs observed in animals following acute administration of fentanyl are typical of opioid analgesics. These include increased motor activity, increased muscle tone and circling, Straub tail and mydriasis for rodents; and decreased motor activity and responsiveness to painful stimuli, ataxia, bradycardia, respiratory depression, salivation, and defecation in dogs. Convulsions occur in rodents and dogs at high doses.

An acute oral toxicity study with fentanyl citrate conducted in dogs at a dose of 35 mg/kg showed bradypnea, flaccid muscle tone, postural abnormalities, pale oral mucosa and conjunctiva and loss of response to sound and touch. One animal also showed tonic convulsion, twitching, mydriasis, coma and loss of light reflex whereas another also appeared with miosis and somnolence. These symptoms had disappeared by day 4 post administration.

Repeat-dose toxicity studies of fentanyl have been described in rats (intramuscular, intravenous), rabbits (topical), and dogs (intramuscular, intravenous). There was no evidence of any target-organ toxicity in any species. In dogs given fentanyl intravenously for 4 weeks, mild cholestasis was observed at 1 mg/kg/day, which is consistent with known biliary effects of opioids.

Genotoxicity

Fentanyl showed no evidence of genotoxicity in the Ames Salmonella mutagenicity assay, in the primary rat hepatocyte unscheduled DNA synthesis assay, in the BALB/c 3T3 transformation test, or in the human lymphocyte and CHO chromosomal aberration *in vitro* assays.

When subjected to genotoxicity testing fentanyl showed no genotoxic activity in the Bacterial Reverse Mutation Assays (*Salmonella* and *E.Coli*), in the *in vitro* mouse lymphoma mutagenesis assay, or in the *in vivo* micronucleus assay in mice.

Like other opioids fentanyl showed mutagenic effects *in vitro* in mammalian cells. A mutagenic risk with therapeutic use seems unlikely since effects were induced only at very high concentrations.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Reproduction Toxicity

No impairment of fertility was observed in rat administered subcutaneous fentanyl at doses of up to 0.5 mg/kg/day. The literature contains reports on the potential effects of fentanyl on embryo-fetal development in the mouse, rat, rabbit and sheep. No evidence of fentanyl teratogenicity was found in mice. Administration of fentanyl to pregnant female Sprague-Dawley rats (0, 10, 100, or 500 µg/kg/day) from day 14 prior to gestation and during the entire gestational period did not produce any evidence of teratogenicity, the high dose being approximately 6-fold the human dose of 800 µg every 6 hours on a mg/m^2 basis.

Teratological effects of fentanyl on rats receiving subcutaneously fentanyl at daily doses of 0.04, 0.08, 0.16 and 0.31 mg/rat showed dose-related maternal toxicity but no congenital abnormalities.

In sheep, epidural administration of fentanyl at doses of 50 to 100 µg/kg from days 124-238 of gestation had no effect on uterine blood flow and tone. Furthermore, there were no cardiovascular or acid-base effects in maternal or foetal sheep for up to 2 hours post-drug epidural administration.

Local Tolerance

No irritation was observed in an evaluation of the irritation potential of representative formulations of Abstral on the oral mucosa in guinea pigs. Repeated administration of a representative placebo formulation of Abstral was conducted in the Syrian hamster cheek pouch model to assess the irritation potential of the tablet's excipients and showed no evidence of tissue irritation upon histological examination.

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PART III: CONSUMER INFORMATION

[N]ABSTRAL®
fentanyl citrate sublingual tablets

This leaflet is part III of a three-part "Product Monograph" published when ABSTRAL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ABSTRAL. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this before you start using Abstral, and every time you get a new prescription. Remember, this information does not take the place of your doctor's instructions.

- **Do not use ABSTRAL unless you are regularly using another opioid pain medicine (for example morphine, fentanyl or hydromorphone) around-the-clock for your background cancer pain.**
- Keep ABSTRAL in a safe place away from children and pets, and to prevent theft, misuse or abuse. Accidental use by a child or pet is a medical emergency and may result in death.
- If a child or pet accidentally uses ABSTRAL, get emergency help right away.
- Do not use the ABSTRAL tablet if the blister pack is broken.
- Do not use ABSTRAL in front of children.
- Make sure you read the **PROPER USE OF THIS MEDICATION** and **WARNING AND PRECAUTIONS** sections. Follow the instructions and always use ABSTRAL the right way. ABSTRAL can cause serious breathing problems and death, especially if it is used the wrong way.
- Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ABSTRAL

ABSTRAL is a tablet taken under the tongue that contains fentanyl.

Never give ABSTRAL to anyone else, even if they have the same symptoms you have. It may harm them and even cause death.

Fentanyl, like all other opioids, is a very strong narcotic pain medicine that can cause <u>serious and life-threatening breathing problems</u> because of an overdose or if the dose you are using is too high for you. Get emergency medical help immediately if you:

- have trouble breathing, or have slow or shallow breathing
- have a slow heartbeat
- have severe sleepiness
- have cold, clammy skin
- feel faint, dizzy, confused, or cannot think, walk or talk normally
- have a seizure
- have hallucinations

ABOUT THIS MEDICATION

<u>IMPORTANT</u>

ABSTRAL can cause serious breathing problems that can progress to death. Read this information carefully before you take ABSTRAL and every time you get a new prescription.

<u>What the medication is used for:</u>

<u>Adults</u>

ABSTRAL is a strong prescription pain medicine that is used to relieve the sudden flares of pain that can occur unexpectedly, while you are taking regular doses of opioid pain killers for your constant cancer pain.

Those sudden flares of pain are described as "breakthrough pain" because they happen or break through your regularly taken opioid pain killers for your constant cancer pain, and usually last for a short while.

<u>What it does:</u>

ABSTRAL is a prescription medicine that contains "fentanyl" which belongs to a class of medicines called "opioids". Opioids are the strongest pain medicines available. ABSTRAL is a tablet that should be placed on the floor of the mouth under your tongue, where it will dissolve rapidly to deliver fentanyl quickly in your bloodstream. This convenient way gives you pain relief starting as early as 10 min after administration.

<u>When it should not be used:</u>

- **Do not use ABSTRAL unless you are using another opioid pain medication regularly for your cancer pain and your body is used to this medicine (opioid tolerant).**
- Do not use ABSTRAL if you have severe problems with your breathing or your lungs.
- Do not use ABSTRAL if you know you are allergic to fentanyl, other opioid-type pain medications, or any of the non-medicinal ingredients (see **What the nonmedicinal**

ingredients are).

- Do not use ABSTRAL if you are currently taking monoamine-oxidase (MAO) inhibitors (used for severe depression) or have done so in the past 2 weeks.
- **Do not take ABSTRAL if it hasn't been prescribed for you as it may harm you or even cause death.**

Pediatrics :
ABSTRAL is not indicated, and should not be used, in children under 18 years of age as safety and efficacy have not been established in patients below this age.

What the medicinal ingredient is:

Fentanyl

What the nonmedicinal ingredients are:

Croscarmellose sodium, mannitol, silicified microcrystalline cellulose and magnesium stearate.

What dosage forms it comes in:

ABSTRAL comes as a small tablet that can easily be placed under your tongue. It is supplied in blister cards, divided into blister units that contain individual tablets.

ABSTRAL tablets come in a range of different strengths, shapes and packaging colors. Your doctor will prescribe the strength (shape) and number of tablets suitable for you. The different strengths and shapes are described below.

Tablet Strength (fentanyl as fentanyl citrate)	**Tablet Shape**	**Packaging Colour**
100 micrograms	Round	Light blue
200 micrograms	Oval	Dark orange
300 micrograms	Triangle	Brown
400 micrograms	Diamond	Violet
600 micrograms	"D"	Turquoise
800 micrograms	Capsule-shaped	Indigo (dark blue)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Serious adverse reactions, including death can occur if you take ABSTRAL without being opioid-tolerant, i.e. if you have not regularly used other opioid medicines for your cancer pain before you start taking ABSTRAL for your sudden flares of pain. ABSTRAL is not indicated for you if you use opioids only intermittently, on an as needed basis.

- You or a family member should call your doctor or get emergency medical help immediately if you have trouble breathing, drowsiness with slow breathing, slow shallow breathing (little chest movement with breathing) or feel faint, dizzy, confused, or have other unusual symptoms. These can be symptoms of an overdose with ABSTRAL. Your dose of ABSTRAL may be too high for you. These symptoms may lead to serious problems or death if not treated immediately. If you have any of the above symptoms, do not take another dose of ABSTRAL.

- You must begin treatment with ABSTRAL at the lowest dose of 100 mcg.

- You must not take more than one dose of ABSTRAL for each episode of breakthrough cancer pain. You must wait at least two hours before treating a new episode of breakthrough pain with ABSTRAL.

- ABSTRAL contains a medicine that can be fatal to children, to any other adult for whom it is not prescribed, and to those who are not regularly taking opioid medicine for their cancer pain.

- Tell your doctor about all the medicines you take and consult with your doctor before taking any new medications while taking ABSTRAL. Some other medications that you may be using can affect the level of ABSTRAL in your body and this may potentially cause respiratory problems and death.

BEFORE you use ABSTRAL talk to your doctor or pharmacist about all of your medical and mental health problems, especially if you have**:**

- trouble breathing or lung problems such as asthma, wheezing or being short of breath
- head injury or brain problem
- liver or kidney problems
- seizures (convulsions or fits)
- slow heart rate or other heart problems
- low blood pressure

- mental health problems such as major depression or hallucinations (seeing or hearing things that are not real)
- a past or present drinking problem or alcoholism for you or a member of your family.
- Past or present drug abuse or addiction problems for you or a family member.

Tell your doctor if you are:

- **pregnant or planning to become pregnant.** ABSTRAL may cause serious harm to your unborn baby.
- **breast feeding.** Fentanyl can pass through your body into breast milk and it could cause serious harm to your baby. ABSTRAL passes through your breast milk. It can cause serious harm to your baby. **You should not use ABSTRAL while breast feeding.**

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Some medicines may cause serious or life-threatening medical problems when taken with ABSTRAL.

Sometimes the doses of certain medicines and ABSTRAL may need to be changed if used together.

- **Do not start taking any medicine while using ABSTRAL** until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using ABSTRAL.

- **Be very careful about taking other medicines that make you sleepy**, such as other pain medicines or some depression medicines (antidepressants that make you sleepy), sleeping pills, anxiety medicines, tranquilizer medicines, or some allergy medicines (antihistamines that make you sleepy).

- **Do not drive or operate machinery or do other dangerous activities** until you know how ABSTRAL affects you as it can make you sleepy.

- **Do not drink alcohol while using ABSTRAL** as it can increase your chance of having dangerous side effects

Know the medicines you take. Keep a list of your medicines to show your doctor and pharmacist.

INTERACTIONS WITH THIS MEDICATION

Interactions can occur between ABSTRAL and other drugs that use a system called CYP 3A4 in the body. Before taking ABSTRAL, tell your doctor about any other medications that you are using including certain antidepressants (selective serotonin reuptake inhibitors (SSRI) and serotonin/norepinephrine reuptake inhibitors (SNRI)). Your prescribed dose will have to be increased or decreased accordingly.

PROPER USE OF THIS MEDICATION

Take ABSTRAL exactly as prescribed. Do not take ABSTRAL more often than prescribed.

You must already be taking another opioid medication before beginning to use ABSTRAL.

You doctor will determine the strength of ABSTRAL you need based on your own particular needs. Do not change your dose without consulting your doctor.

IMPORTANT:

- Follow the instructions of your doctor carefully, as he will adjust your dose gradually until you have satisfactory pain relief.
- Do not skip ahead to a higher dose.
- You must not take more than one dose of ABSTRAL for each episode of breakthrough cancer pain.
- You must wait at least 2 hours before treating another episode of breakthrough cancer pain with ABSTRAL.
- Do not use ABSTRAL for more than four episodes of breakthrough cancer pain in one day.

STARTING DOSE

All patients MUST begin treatment using one 100 mcg ABSTRAL tablet.

SUBSEQUENT DOSES

To find the right dose for you, your doctor will instruct you on how to safely increase your dose until you have reached a dose, which provides you with adequate pain relief within 30 minutes, and if there are side effects that they are acceptable to you.

Following is a step by step guide for safely increasing your dose of ABSTRAL that your doctor will explain to you:

- Your doctor will change the dose until you and your doctor find the right dose for you.
- You must not use more than one dose of ABSTRAL for each episode of breakthrough cancer pain:
  - Take 1 dose for an episode of breakthrough cancer pain.
  - If the pain does not get better 30 minutes after taking the first dose of ABSTRAL, you can take other rescue medication (but not ABSTRAL) as discussed with your doctor.
- Wait at least 2 hours before treating a new episode of breakthrough cancer pain with ABSTRAL.
- Remember to keep taking your regular background opioid pain medicine while taking ABSTRAL.

Your doctor will monitor your reaction to the increases in ABSTRAL dose as well as any side effects that you may experience.

Your doctor will provide you with a prescription to treat up to four breakthrough pain episodes per day by using the identified dose.

If you have more than four episodes of breakthrough pain in one day talk to your doctor as your regular opioid medicine for your constant cancer pain may need to be changed.

HOW TO USE YOUR ABSTRAL TABLET:

ABSTRAL tablets come in blister packages. Do not open the blister until ready to use.

Once opened, use ABSTRAL tablet right away.

The ABSTRAL tablet should be placed on the floor of the mouth under your tongue, where it will dissolve rapidly and be absorbed into your body through the lining of your mouth. Once absorbed, fentanyl starts to work to relieve pain.

Do NOT suck, chew or swallow the tablet(s).

When you get an episode of breakthrough pain, take the dose advised by your doctor as follows:

- If your mouth is dry, take a sip of water to moisten it. Spit out or swallow the water. Dry your hands if they are wet before you handle ABSTRAL tablets.
- ABSTRAL comes in a blister package. Each blister unit contains an ABSTRAL tablet. It is important that the tablet stays sealed in the blister unit until you are ready to use it. (see Figure 1)
- When you are ready to take a tablet, pull apart one of the blister units from the blister card by tearing along the dotted lines (perforations). (see Figure 2)

Figure 1

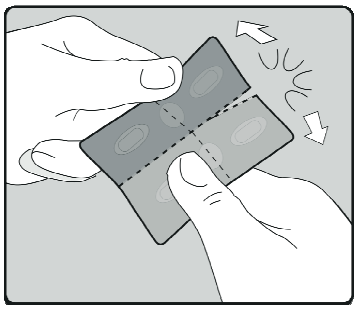
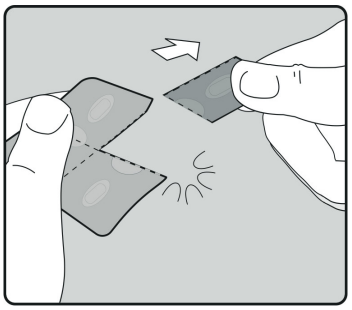


Figure 2



- When the blister unit is fully separated, (see Figure 3)
- Peel back the foil starting at the unsealed area where indicated and gently remove the tablet. **Do not try to push ABSTRAL tablets through the foil.** This will damage the tablet. (see Figure 4)

Figure 3

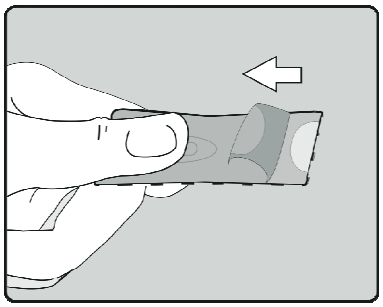
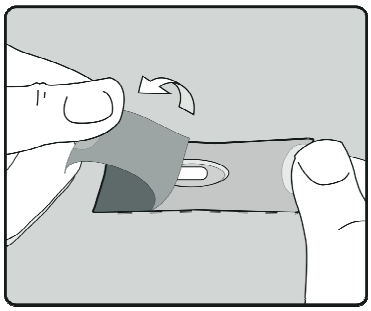


Figure 4



- As soon as you remove the tablet from the blister, place it on the floor of your mouth under your tongue, as far back as you can, (see Figures 5, 6 and 7) and let it dissolve completely. If more than one tablet is required, spread them around the floor of your mouth under your tongue. ABSTRAL will dissolve rapidly under the tongue and be absorbed in order to provide pain relief. It is therefore important that you do not suck, chew or swallow the tablet.

Figure 5

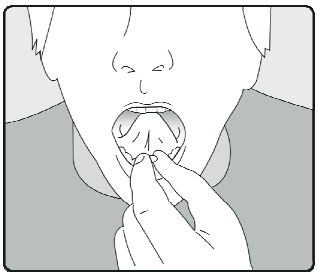


Figure 6

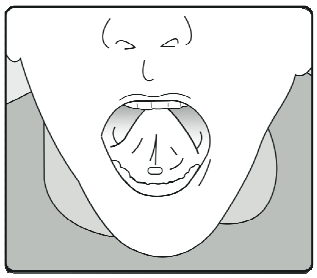
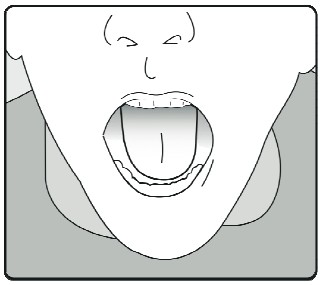


Figure 7



- You should not drink or eat anything until the tablet has completely dissolved under your tongue and you can no longer feel it in your mouth.

- **Do not use more than 4 tablets simultaneously per dose.**

Overdose:

If you accidentally take more than your prescribed dose of ABSTRAL, seek emergency medical help by contacting your regional poison control centre or by calling 911 immediately.

In cases of possible overdose, try to remove the tablet or any parts of it still remaining in the mouth.

Overdose with an opioid medicine such as ABSTRAL can cause serious problems, the most serious being trouble breathing, extreme drowsiness with slowed breathing, and slow shallow breathing. Other signs of fentanyl overdose may include tiredness, extreme sleepiness or sedation; inability to think, talk or walk normally; and feeling faint, dizzy or confused, seizure and hallucination.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, ABSTRAL may cause unwanted effects.

The most common side effects of ABSTRAL are nausea, vomiting, constipation, dry mouth, somnolence dizziness, headache, tiredness and short breath.

These are common side effects of opioid pain medicines like ABSTRAL. Talk to your doctor about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking ABSTRAL.

- **ABSTRAL can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.
- **ABSTRAL can cause physical dependence if taken regularly.** Do not stop taking ABSTRAL or any other opioid without talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
- There is a chance of abuse or addiction with ABSTRAL. The chance is higher if you are or have previously been addicted to or abused other medications, street drugs, or alcohol, or if you have a history of mental health problems. Your doctor can advise you on these risks.

Talk with your doctor about any side effects that bother you or do not go away. These are not all the side effects of ABSTRAL. For more information, ask your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

You or a family member should **call your doctor or get emergency medical help immediately** if you have any of the symptoms below:

- trouble breathing
- extreme drowsiness with slowed breathing
- slow, shallow breathing (little chest movement with breathing)
- feel faint, dizzy or confused
- inability to think, talk or walk normally
- seizure and hallucination

These can be symptoms of an overdose of ABSTRAL. Your dose of ABSTRAL may be too high for you. **These symptoms may lead to serious problems or death if not treated immediately. If you have any of these symptoms, do NOT take any more ABSTRAL until you have seen your doctor.**

In cases of possible overdose try to remove ABSTRAL tablets or any parts of it still remaining in the mouth.

This is not a complete list of side effects. For any unexpected effects while taking ABSTRAL, contact your doctor or pharmacist.

HOW TO STORE IT

- **Keep ABSTRAL in a safe place away from children.**

- Store ABSTRAL at room temperature between 15° and 30°C (59°-86° F) and in the original blister to protect from moisture until ready to use. Do not use if the blister package has been opened.

The amount of fentanyl contained in an ABSTRAL tablet can be fatal to a child. The entire ABSTRAL tablet should be used immediately after opening the child-resistant package. Patients and their caregivers must be instructed to keep ABSTRAL out of the reach of children.

How to dispose of ABSTRAL tablets when no longer needed

Bring all unused ABSTRAL tablets to your pharmacist for proper disposal.

Or

Dispose of unopened ABSTAL blisters as soon as you no longer need them by flushing them down the toilet:

1. Remove the ABSTRAL tablet from its blister package.
2. Drop the ABSTRAL tablet into the toilet.
3. Repeat steps 1 and 2 for each ABSTRAL blister. Flush the toilet after all unneeded blisters have been put into the toilet.

- Do not flush the ABSTRAL blister packages or cartons down the toilet.

General Information

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use ABSTRAL for a condition for which it was not prescribed. Do not give ABSTRAL to other people, even if they have the same symptoms you have. It may harm them. The leaflet summarizes the most important information about ABSTRAL. If you would like more information, talk with your healthcare provider. You can also call PALADIN LABS INC. at: 1-888-550-6060.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid label, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.paladinlabs.com
or by contacting the sponsor, Paladin Labs Inc., at:
1-888-550-6060

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