

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1049/006/001

Case No: 2059445

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

ProStrakan Limited

Galabank Business Park, Galashiels, TD1 1QH, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Abstral 50 microgram sublingual tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **29/09/2009** until **21/05/2014**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Abstral 50 microgram sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains:

50 micrograms fentanyl (as citrate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet

50 microgram sublingual tablet is a white pentagon-shaped tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

4.2 Posology and method of administration

Abstral should only be administered to patients who are considered tolerant to their opioid therapy for persistent cancer pain. Patients can be considered opioid tolerant if they take at least 60 mg oral morphine per day, 25 micrograms transdermal fentanyl per hour, or an equianalgesic dose of another opioid for a week or longer.

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

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

Dose titration:

The object of dose titration is to identify an optimal maintenance dose for ongoing treatment of breakthrough pain episodes. This optimal dose should provide adequate analgesia with an acceptable level of adverse reactions.

The optimal dose of Abstral will be determined by upward titration, on an individual patient basis. Several doses are available for use during the dose titration phase. The initial dose of Abstral used should be 100 micrograms, titrating upwards as necessary through the range of available dosage strengths.

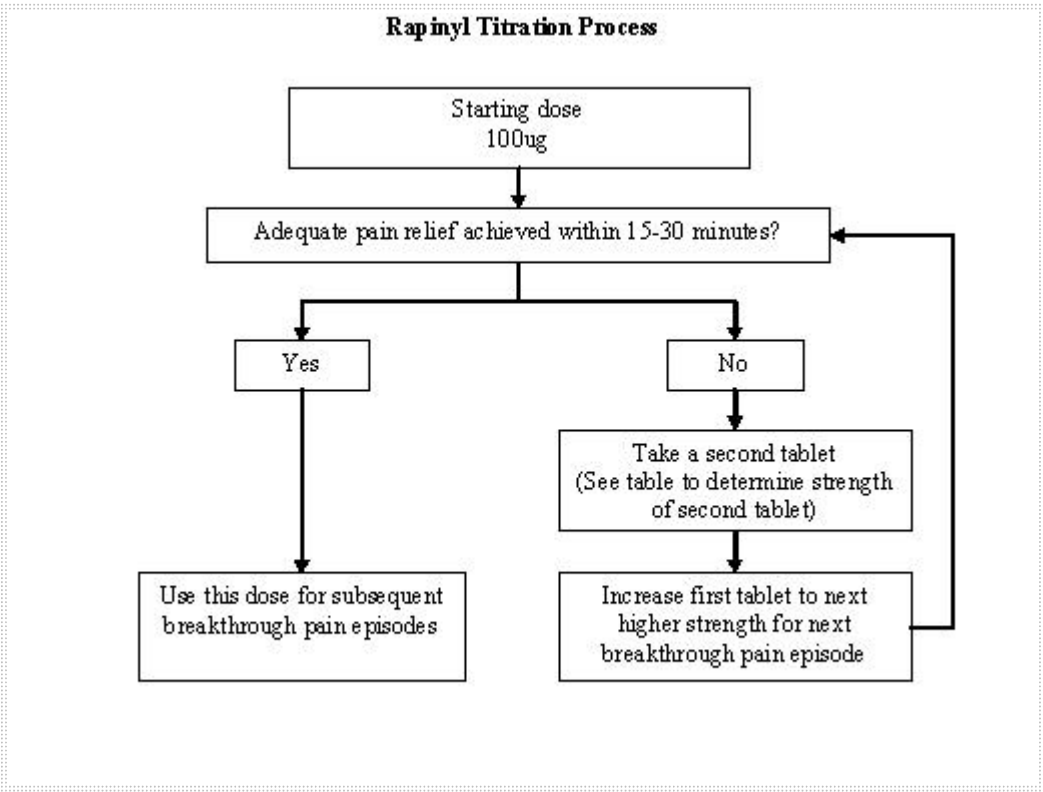
Patients should be carefully monitored until an optimal dose is reached.

Switching from other fentanyl containing products to Abstral must not occur at a 1:1 ratio because of different absorption profiles. If patients are switched from another fentanyl containing product, a new dose titration

with Abstral is required.

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

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



Strength (micrograms) of first sublingual tablet per episode of breakthrough pain	Strength (micrograms) of supplemental (second) sublingual tablet to be taken 15-30 minutes after first tablet, if required
100	100
200	100
300	100
400	200
600	200
800	-

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

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

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

Maintenance therapy:

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

Dose re-adjustment:

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

If more than four episodes of breakthrough pain are experienced per day over a period of more than four consecutive days, then the dose of the long acting opioid used for persistent pain should be re-evaluated. If the long acting opioid or dose of long acting opioid is changed the Abstral dose should be re-evaluated and re-titrated as necessary to ensure the patient is on an optimal dose.

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

Discontinuation of therapy:

For patients no longer requiring any opioid therapy, the Abstral dose should be taken into consideration before a gradual downward titration of opioids to minimise possible withdrawal effects.

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

Use in children and adolescents:

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

Use in elderly patients

Dose titration needs to be approached with particular care and patients observed carefully for signs of fentanyl toxicity (see section 4.4).

Use in patients with renal and hepatic impairment

Patients with kidney or liver dysfunction should be carefully observed for signs of fentanyl toxicity during the Abstral titration phase (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Opioid-naïve patients because of the risk of life-threatening respiratory depression.

Severe respiratory depression or severe obstructive lung conditions.

4.4 Special warnings and precautions for use

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

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

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

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

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

Abstral should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of hyperkapnia, such as those showing evidence of raised intracranial pressure, reduced consciousness, coma or brain tumours. In patients with head injuries, the clinical course may be masked by the use of opioids. In such a case, opioids should be used only if absolutely necessary.

Intravenous fentanyl has been shown to cause bradycardia. Abstral should be used with caution in patients with bradyarrhythmias.

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant use of other CNS depressants, such as other morphine derivatives (analgesics and antitussives), general anaesthetics, skeletal muscle relaxants, sedative antidepressants, sedative H1 antihistamines, barbiturates, anxiolytics (ie benzodiazepines), hypnotics, antipsychotics, clonidine and related substances may produce increased CNS depressant effects. Respiratory depression, hypotension and profound sedation may occur.

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

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

The concomitant use of partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients.

4.6 Pregnancy and lactation

The safety of fentanyl in pregnancy has not been established. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Fentanyl should only be used during pregnancy when clearly necessary.

Long-term treatment during pregnancy may cause withdrawal symptoms in the new-born infant.

Fentanyl should not be used during labour and delivery (including caesarean section) since fentanyl crosses the placenta and may cause respiratory depression in the foetus or in the new-born infant.

Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should only be used by breast-feeding women if the benefits clearly outweigh the potential risks for both mother and child.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Undesirable effects typical of opioids are to be expected with Abstral; they tend to decrease in intensity with continued use. The most serious potential adverse reactions associated with opioid use are respiratory depression (which could lead to respiratory arrest), hypotension and shock. Other very commonly reported adverse reactions include: nausea, vomiting, constipation, headache, somnolence/fatigue and dizziness.

Adverse reactions from clinical studies with Abstral in patients and volunteers, with a suspected relationship to treatment, are listed below by system organ class and frequency (very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders

Very common: Dizziness, somnolence, headache

Common: Vasovagal reaction, hypoaesthesia, paraesthesia, hyperacusis

Eye disorders

Common: Vision abnormal

Respiratory, thoracic and mediastinal disorders

Common: Respiratory depression, rhinitis, pharyngitis

Gastrointestinal disorders

Very common: Nausea

Common: Vomiting, abdominal pain, diarrhoea, constipation, stomach discomfort, dyspepsia, dry mouth

Skin and subcutaneous tissue disorders

Common: Rash, pruritus

Vascular disorders

Common: Orthostatic hypotension, flushing, hot flush

General disorders and administration site conditions

Very common: Fatigue

Common: Asthenia, application site irritation

Psychiatric disorders

Common: Depression, anorexia, concentration impaired, euphoria

All the above adverse reactions were reported in opioid naïve volunteers administered with Abstral. Patients (n=23) treated with Abstral only experienced dizziness, nausea and vomiting.

The following adverse reactions associated with other medicinal products containing fentanyl have also been reported (very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1000$ to $< 1/100$; rare $\geq 1/10,000$ to $< 1/1000$; very rare $< 1/10,000$; not known (cannot be estimated from available data)):

Cardiac disorders

Uncommon: Bradycardia, tachycardia, hypertension

Very rare: Arrhythmias

Nervous system disorders

Common: Myoclonus, insomnia, taste disorders

Uncommon: Abnormal gait/coordination, vertigo, amnesia, speech disorders, tremor

Respiratory thoracic and mediastinal disorders

Uncommon: Hypoventilation, asthma, dyspnoea,

Very rare: Apnoea, haemoptysis

Gastrointestinal disorders

Common: Gastro-intestinal occlusion, dysphagia, mouth ulcers/stomatitis, tongue disorder

Uncommon: Enlarged abdomen, flatulence, thirst

Rare: Hiccups

Renal and urinary disorders

Uncommon: Urinary retention, change in urinary frequency

Very rare: bladder spasm, oliguria

Skin and subcutaneous tissue disorders

Very common: Sweating

Injury, poisoning and procedural complications

Common: Accidental injuries

Vascular disorders

Common: Vasodilation

General disorders and administration site conditions

Uncommon: Malaise

Psychiatric disorders

Common: Hallucinations, confusion, anxiety, nervousness, abnormal thinking, abnormal dreams

Uncommon: Agitation, depersonalisation, emotional lability

4.9 Overdose

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

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

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Phenylpiperidine derivatives.

ATC code: N02AB03

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

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

In patients with chronic cancer pain on stable maintenance doses of opioids, Abstral has been shown to induce significantly superior relief of breakthrough pain compared to placebo from 15 minutes after administration onwards, with a significantly lower need for rescue analgesic therapy. The safety and efficacy of Abstral have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. Preemptive use of Abstral for predictable pain episodes was not investigated in the clinical trials.

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

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

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

5.2 Pharmacokinetic properties

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

Abstral is a quick dissolving sublingual tablet formulation. Rapid absorption of fentanyl occurs over about 30 minutes following administration of Abstral. The bioavailability of Abstral has not been studied but is estimated to be about 70%. Mean maximal plasma concentrations of fentanyl range from 0.2 to 1.3 ng/ml (after administration of 100 to 800 μ g Abstral) and are reached within 22.5 to 240 minutes.

About 80-85% of fentanyl is bound by plasma proteins, mainly α 1-glycoprotein and to a lesser extent albumin and lipoprotein. The volume of distribution of fentanyl at steady state is about 3-6 l/kg.

Fentanyl is metabolised primarily via CYP3A4 to a number of pharmacologically inactive metabolites, including norfentanyl. Within 72 hours of intravenous fentanyl administration around 75% of the dose is excreted into the urine, mostly as metabolites, with less than 10% as unchanged drug. About 9% of the dose is recovered in the faeces, primarily as metabolites. Total plasma clearance of fentanyl is about 0.5 l/h/kg. After Abstral administration, the main elimination half-life of fentanyl is about 7 hours (range 3-12.5 hours) and the terminal half-life is about 20 hours (range 11.5-25 hours).

The pharmacokinetics of Abstral have been shown to be dose proportional over the dose range of 100 to 800 μ g.

Renal/hepatic impairment

Impaired hepatic or renal function could cause increased serum concentrations. Elderly, cachectic or generally impaired patients may have a lower fentanyl clearance, which could cause a longer terminal half-life for the compound (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Safety pharmacology and repeated dose toxicity data reveal no special hazard for humans that is not already covered by other sections of this SPC. Animal studies have shown reduced fertility and increased mortality in rat foetuses. Teratogenic effects have, however, not been demonstrated.

Mutagenicity testing in bacteria and in rodents yielded negative results. 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.

Long-term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Silicified microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

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

6.5 Nature and contents of container

Abstral sublingual tablets are packaged in OPA/PVC/aluminium/aluminium blisters contained in a cardboard outer carton. The packaging is colour-coded for each Abstral sublingual tablet strength.

Pack size: Packs of 10 or 30 sublingual tablets. Not all pack sizes may be marketed

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

ProStrakan Ltd
Galabank Business Park
Galashiels TD1 1QH
UK

8 MARKETING AUTHORISATION NUMBER

PA1049/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 22nd May 2009

10 DATE OF REVISION OF THE TEXT

September 2009