PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine is to be supplied upon a doctor's prescription only

Abstral® 100 mcg
Abstral® 200 mcg
Abstral® 300 mcg
Abstral® 400 mcg
Abstral® 600 mcg
Abstral® 800 mcg

Sublingual tablets

Composition:
Each tablet contains:
The active ingredient and its quantity:
Abstral 100 mcg: Fentanyl (as citrate) 100 mcg
Abstral 200 mcg: Fentanyl (as citrate) 200 mcg
Abstral 300 mcg: Fentanyl (as citrate) 300 mcg
Abstral 400 mcg: Fentanyl (as citrate) 400 mcg
Abstral 600 mcg: Fentanyl (as citrate) 600 mcg
Abstral 800 mcg: Fentanyl (as citrate) 800 mcg

Inactive ingredients and allergens: see section 6 of this leaflet: **"Additional information".**

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their illness is similar to yours. This medicine is intended for adults above 18 years of age.

- Taking this medicine with benzodiazepines or other medications which suppress the central nervous system (including narcotics) or alcohol may result in profound sedation, breathing difficulties (respiratory depression), coma and death.
- Opiates could cause addiction, especially in prolonged use, and may potentially lead to abuse and overdose. A response to overdose could result in slow breathing and even cause death. Make sure you know the name of the medicine, the dose you are taking, administration frequency, duration of treatment, side effects and potential risks. Additional information related to the risk of dependence and addiction can be found at the following link: https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_en.pdf

1. What is the medicine intended for?

Abstral is intended for the treatment of breakthrough pain in oncologic patients who are treated with strong pain-relief medicines (opioids) regularly.

Breakthrough pain is pain which occurs suddenly, even though you are using your opioid pain-relief medicine regularly.
Therapeutic group: The active ingredient in Abstral sublingual tablets is fentanyl. Fentanyl belongs to a group of strong narcotic pain-relief medicines called opioids.

2. Before using this medicine

X Do not use the medicine:
- If you are hypersensitive (allergic) to the active ingredient fentanyl or to any of the other ingredients of this medicine (listed in section 6).
- If you suffer from severe breathing problems.
- If you are not regularly using a prescribed opioid medicine every day on a regular schedule, for at least a week, to control your persistent pain (e.g. opioids such as codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine). If you are not using these medicines you **must not** use Abstral because it may increase the risk of dangerously slow and/or shallow breathing, or even cessation of breathing.
- If you suffer from short-term pain other than breakthrough pain.
- If you are treated with medications containing sodium oxybate.

! Special warnings about using this medicine
Tell your doctor or pharmacist before treatment if you suffer or have suffered in the past from any of the following conditions, as your doctor will need to take this into account when adjusting your dosage:
- a head injury, because Abstral may mask the extent of the injury.
- breathing problems or if you suffer from muscle weakness disease (myasthenia gravis).
- if you have heart problems, especially if you suffer from slow heart rate.
- low blood pressure.
- liver or kidney disease, as this may require your doctor to adjust your dosage more carefully.
- a brain tumor and/or increase in intracranial pressure (increased pressure in the brain which causes severe headaches, nausea/vomiting and blurred vision).
- mouth wounds or mucositis (swelling and redness of the inside of the mouth).
- if you take antidepressants or antipsychotics, please read the next section, "Other medicines and Abstral", carefully.
- if you have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use.

When taking Abstral, inform your doctor or dentist that you are taking this medicine, if:
- you are about to have any surgery.
- you experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of your medicine as prescribed by your doctor.
- you experience a combination of the following symptoms: nausea, vomiting, anorexia, fatigue, weakness, dizziness and low blood pressure. Combination of these symptoms may be a sign of a potentially life-threatening condition called

adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones.

Your doctor may need to check you more carefully if:

- you or someone of your family members have ever abused or suffered from dependence on alcohol, prescription drugs or illicit drugs ("addiction")
- you are a smoker
- If you have suffered from mood problems (depression, anxiety or personality disorder) or have been treated by a psychiatrist due to other mental illnesses

Repeated use of Abstral may lead to dependence and abuse, which may lead to a life-threatening overdose. It is important for you to consult with a doctor if you are concerned that you may develop Abstral dependence.

Sleep related breathing problems

Abstral may cause sleep related breathing problems, such as sleep apnea (breathing cessations while sleeping) and hypoxemia during sleep (low blood oxygen level). Possible symptoms are: breathing cessations while sleeping, awakening at night due to shortness of breath, difficulty to continue sleeping or increased somnolence during daytime. If you or anyone else have noticed these symptoms, contact the doctor. The doctor may consider dose reduction.

Other medicines and Abstral

Please tell your doctor or pharmacist if you are taking, or have recently taken any other medicines, including non-prescription drugs and food supplements.

Some medicines may increase or decrease the effects of Abstral. Therefore if you start, change the dose of, or stop therapy with the following medications, tell your doctor as he may need to adjust your dose of Abstral:

- Antifungal medicines used to treat fungal infections, e.g. ketoconazole or itraconazole.
- Antibiotics of the macrolides group used to treat infections, e.g. erythromycin.
- Antiviral medicines of the protease inhibitors class used to treat infections caused by viruses, e.g. ritonavir.
- Rifampin or rifabutin (medicines used to treat bacterial infections).
- Carbamazepine, phenytoin or phenobarbital (medicines used to treat convulsions/seizures).
- Herbal medicines containing St John's wort *(Hypericum perforatum*).
- Medicines containing alcohol.
- Medicines of the monoamine-oxidase inhibitors (MAOI) class, which are used to treat severe depression and Parkinson's disease. Tell your doctor if you have taken this type of medicine within the last two weeks.
- Certain types of strong pain killers, called partial agonists/antagonists e.g. buprenorphine, nalbuphine and pentazocine. You could experience symptoms of withdrawal syndrome (e.g. nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating) while using these medicines.

Abstral may enhance the anesthetic effect of the following medicines (sedatives), and in addition, increase the risk of respiratory depression and decrease in blood pressure:

- Other strong pain-relief medicines (medicines of the opioid class for relief of pain or cough)
- General anaesthetics (used to make you sleep during operations)
- Muscle relaxants
- Sleeping medicines
- Medicines used to treat:
  - Depression
  - Allergies (sedative antihistamines - H1 blockers)
  - Anxiety and psychosis (medicines of the barbiturates class, benzodiazepines, e.g. diazepam, hypnotics (which induce sleep) or antianxiety medicines)
- Medicines containing clonidine (used to treat high blood pressure)

Use of Abstral concomitantly with medicines causing you to feel sleepy (sedatives), such as benzodiazepines, increases the risk of somnolence, breathing difficulties (respiratory depression), coma and may be life-threatening. Therefore, use of Abstral together with sedatives should be considered only when there are no other treatment options.

However, if you doctor decides to use Abstral together with sedatives anyway, the dose and treatment duration should be limited by the doctor.

Please tell your doctor about any sedatives you are taking and carefully follow the dose recommended by the doctor. It may be useful to inform your friends or relatives to make them aware of the aforementioned signs and symptoms. Contact your doctor when you experience such symptoms.

The risk of certain other side effects increases if you are taking medicines such as antidepressants or antipsychotics, since drug interaction may occur, manifested by mental state changes [e.g. agitation (restlessness), hallucinations, coma], and other effects such as high temperature above 38°C, increase in heart rate, unstable blood pressure and enhanced reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). In this case, your doctor will advise you whether Abstral is suitable for you.

Using this medicine with food and drink
Grapefruit juice may increase the risk of side effects of Abstral, therefore do not drink grapefruit juice while you are treated with Abstral.

Using this medicine and alcohol consumption
Abstral may make some patients feel drowsy. Do not consume alcohol while you are treated with this medicine without consulting your doctor as it might make you feel more drowsy than usual.

Pregnancy and breastfeeding
You must not use Abstral if you are pregnant, unless you have been explicitly told otherwise by your doctor, since fentanyl may cause withdrawal symptoms in the newborn and endanger its life.
Do not breastfeed during treatment with Abstral, and do not start breastfeeding until at least 5 days after the last dose of Abstral. Fentanyl can pass into breast milk and may cause sedation and respiratory depression in the breastfed infant.
If you are pregnant or breastfeeding, consult your doctor or pharmacist before taking any medicines.

Driving and using machines
Abstral may impair your mental and/or physical ability to perform potentially hazardous tasks such as driving or operating machinery.
If you feel dizzy, sleepy or have blurred vision when you take Abstral, do not drive or operate machinery.

Abstral contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to use this medicine?
Before starting treatment with Abstral, your doctor will explain how Abstral should be taken to effectively relieve your breakthrough pain.
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure.
This product should **only** be used by you according to your doctor's instructions. **The product should not be used by anyone else except you, as it may be associated with a serious risk to their health, especially in children.**
Abstral is different from other medicines you may have previously taken to treat breakthrough pain. **You must always take Abstral at the dose prescribed by your doctor** – this dose may be different from that of other medicines which you have taken **in the past** to treat breakthrough pain.
The dosage and manner of treatment will be determined by the doctor only. The usual recommended dosage is:

Starting treatment – finding the most appropriate dose
For Abstral to work effectively, your doctor will need to identify the most appropriate dose for treating your breakthrough pain. Abstral is available in several dosages. You may need to try different strengths of Abstral over a number of episodes of breakthrough pain to find the most appropriate dose. Your doctor will help you do this and will guide you how to find the most appropriate tablet strength.
If you do not feel adequate pain relief after one dose, your doctor may ask you to take an extra dose to treat an episode of breakthrough pain.

Do not take an additional dose unless your doctor tells you to, as this may result in overdose.

Your doctor may advise you to take a dose which consists of more than one tablet at a time. **Only do this if explicitly directed by your doctor.**

Wait at least 2 hours from taking your last dose of Abstral before taking the next dose to treat another episode of breakthrough pain.

Maintenance dose (continuing treatment) – once you have found the most appropriate dose for you

Once you and your doctor have found a dose of Abstral that controls your breakthrough pain, you should take this dose no more than four times a day. **A dose of Abstral may consist of more than one tablet.**

Wait at least 2 hours from taking your last dose of Abstral before taking the next dose to treat another episode of breakthrough pain.

If you think that the dose of Abstral that you are taking is not controlling your breakthrough pain satisfactorily, tell your doctor, as the dose may need to be adjusted.

Do not change the dose of Abstral unless explicitly directed by your doctor.

Do not exceed the recommended dose.

Directions for use:

Abstral should be used sublingually. Place the tablet under the tongue, where it dissolves rapidly, in order to allow the active ingredient, fentanyl, to be absorbed across the lining of the mouth. Once absorbed, fentanyl starts to relieve the pain.

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

- If your mouth is dry, take a sip of water to moisten it. Spit out or swallow the water.
- Remove the tablet from the blister pack immediately before use as follows:
  - Separate one of the blister squares from the pack by tearing along the dotted lines/perforations (keep the remaining blister squares together).
  - Peel back the edge of the foil in the arrow direction, and gently remove the tablet. Do not try to push a tablet through the foil top, as this may damage it.
- Place the tablet under your tongue as far back as you can and let it dissolve completely.
- Abstral will dissolve rapidly under the tongue, and will be absorbed in order to relieve the pain.

Do not suck, split, crush, chew or swallow the tablet.
Place the entire tablet under your tongue.
You should not drink or eat anything until the tablet has completely dissolved under your tongue.

If you accidently took a higher dose:

- Remove any remaining medicine from your mouth.
- Tell your caregiver or another person what has happened.
- Contact your doctor immediately or proceed to a hospital emergency room and bring the package of the medicine with you. The person accompanying the patient should

keep the patient awake by talking to him or shaking him now and then.

Symptoms of overdose include:
- Extreme drowsiness
- Slow and shallow breathing
- Coma

If these symptoms occur, seek emergency medical help immediately.

If an adult or a child has accidently taken the medicine, he must be immediately referred to a doctor or a hospital emergency room and bring the package of the medicine.

Adhere to the treatment as recommended by your doctor.

If you stop taking this medicine
When you no longer have any breakthrough pain, you can discontinue Abstral, but you must continue using your regular opioid pain-relief medicine to treat your persistent pain as advised by your doctor.
If you stop taking Abstral, you may experience withdrawal symptoms similar to the possible side effects of Abstral.

If you experience withdrawal symptoms or if you are concerned about your pain relief, you should contact your doctor. Your doctor will consider whether you need a medicine to treat the withdrawal symptoms.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects
Like all medicines, using this medicine may cause side effects in some users. Do not be alarmed while reading the list of side effects, you may not experience any of them.

If you feel unusually or extremely sleepy or your breathing becomes slow or shallow, proceed immediately to your doctor or a local hospital for emergency treatment (see also section 3 "If you accidently took a higher dose").
Very common side effects (may affect more than 1 in 10 people):
- Nausea

Common side effects (may affect up to 1 in 10 people):
- Dizziness, headaches, excessive sleepiness
- Breathlessness/shortness of breath
- Inflammation inside the mouth, vomiting, constipation, dry mouth
- Sweating, weariness/tiredness/lack of energy

Uncommon side effects (may affect up to 1 in 100 people):

- Allergic reactions, tremor, disturbed or blurred vision, slow or fast heartbeat, low blood pressure, memory loss
- Depression, suspicious thoughts or feeling afraid for no reason, feeling confused, feeling disorientated, feeling anxious/restless/unhappy, feeling unusually happy (euphoria), mood swings
- Feeling full persistently, abdominal pain, indigestion
- Mouth ulcers, problems with tongue, pain in mouth or throat, tightness in throat, lip or gum ulcers
- Loss of appetite, loss of or change in sense of taste/smell
- Difficulty sleeping or disturbed sleep, lack of attention/easily distracted, lack of energy/weakness
- Skin disorders, rash, itchiness, night sweats, decreased sensitivity to touch, bruising easily
- Joint pain or stiffness, muscle stiffness
- Drug withdrawal symptoms (e.g. nausea, vomiting, diarrhoea, anxiety, chills, tremor, sweating), accidental overdose, in males: an inability to get and/or keep an erection, feeling generally unwell.

Side effects of unknown frequency (frequency cannot be estimated based on the available data):

- Swollen tongue, severe breathing problems, falls, flushing, feeling extremely warm, diarrhoea, seizures (convulsions), swelling of the arms or legs, seeing or hearing things that are not really there (hallucinations), fever, drug dependence (addiction), drug abuse, reduced level or loss of consciousness, itchy rash and delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbances, nightmares).

Prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which may be life-threatening (see section 2).

Reporting side effects
If a side effect appears, if any of the side effects gets worse or if you experience side effects not mentioned in this leaflet, consult your doctor.
Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” that appears on the homepage of the Ministry of Health’s website (www.health.gov.il) which links to an online form for reporting side effects, or by the following link:
https://sideeffects.health.gov.il/
In addition, you can report by emailing the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

5. How to store the medicine

- Prevent poisoning! **Abstral is a very strong pain-relief medicine which may be life-threatening if accidentally taken by a child.** Therefore, this medicine, and any

other medicine, must be stored in a closed **and locked** place out of the reach and sight of children and/or infants, in order to prevent poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

- **It is recommended to keep this medicine in a locked place.**
- Do not use this medicine after the expiry date (exp. date) which is stated on the box and the blister. The expiry date refers to the last day of that month.

- **Storage conditions:** Do not store above 25˚C. Store in the original blister package in order to protect from moisture.
- **How to dispose of unused tablets?** If you have Abstral tablets that are no longer needed, give them to the nearest pharmacy in order to dispose of them safely and protect the environment. Do not throw away any medicines via wastewater or household waste.

6. Additional information

- **In addition to the active ingredient this medicine also contains:**
  Mannitol (E421), Silicified microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate.

- **What the medicine looks like and contents of the pack:**
  Abstral is a small white sublingual tablet to be inserted under the tongue. The tablet comes in a range of different strengths and shapes. Your doctor will prescribe the strength and number of tablets suitable for you.

  Abstral 100 microgram tablet is a white round tablet
  Abstral 200 microgram tablet is a white oval-shaped tablet
  Abstral 300 microgram tablet is a white triangle-shaped tablet
  Abstral 400 microgram tablet is a white diamond-shaped tablet
  Abstral 600 microgram tablet is a white “D”-shaped tablet
  Abstral 800 microgram tablet is a white capsule-shaped tablet

  Abstral is marketed in packs of 10 or 30 tablets. The tablets are packed in blisters.

  Not all pack sizes may be marketed.

- **Registration Holder’s name and address:** Neopharm Ltd., 6 Hashiloach St., P.O.B. 7063, Petach Tikva 4917001.

- **Manufacturer’s name and address:** Kyowa Kirin Ltd., Galashiels, UK.

  Revised in August 2022 according to the Ministry of Health guidelines.

- **Drug registration numbers at the National Medicine Registry of the Ministry of Health:**
  Abstral 100 mcg: 148 73 33262

Abstral 200 mcg: 148 74 33263
Abstral 300 mcg: 148 75 33264
Abstral 400 mcg: 148 76 33265
Abstral 600 mcg: 148 77 33266
Abstral 800 mcg: 148 78 33267