B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

BREAKYL 200 microgram buccal film
BREAKYL 400 microgram buccal film
BREAKYL 600 microgram buccal film
BREAKYL 800 microgram buccal film
BREAKYL 1200 microgram buccal film

Active substance: Fentanyl

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Breakyl is and what it is used for
2. What you need to know before you use Breakyl
3. How to use Breakyl
4. Possible side effects
5. How to store Breakyl
6. Contents on the pack and other information

1. WHAT BREAKYL IS AND WHAT IT IS USED FOR

Breakyl buccal film contains the active substance fentanyl, a strong pain-relieving medicine known as an opioid. Breakyl is indicated for the management of breakthrough cancer pain in adult patients. Breakthrough pain is additional sudden pain. This may occur although you have taken your regular opioid pain relieving medicine.

Breakyl must only be used, if you are already taking and are used to regular opioid therapy like morphine, oxycodone, or transdermal fentanyl for a minimum of one week to treat your chronic cancer pain.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE BREAKYL

Do <u>not</u> use Breakyl:

- if you are allergic (hypersensitive) to fentanyl, or any of the other ingredients of this medicine (listed in section 6).
- if you are currently taking monoamine-oxidase (MAO) inhibitors (used for severe depression) or have done so in the past 2 weeks.
- if you suffer from severe breathing problems or severe obstructive lung conditions (like severe asthma).

- if you are not regularly using a prescribed opioid medicine (e.g. codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine), every day on a regular schedule, for at least a week, to control your persistent pain. If you have not been using these medicines you **must not** use Breakyl, because it may increase the risk that breathing could become dangerously slow and/or shallow, or even stop.
- If you suffer from short-term pain other than breakthrough pain.

Warnings and Precautions
Talk to your doctor before starting Breakyl, if you have any of the following, as your doctor will need to take account of this when prescribing your dose:
- Your other opioid pain medicine taken for your chronic cancer pain is not stabilised yet
- You are suffering from any condition that has an effect on your breathing.
- You have a head injury or if your doctor has diagnosed an increased cranial pressure.
- You have problems with your heart, especially slow heart rate, or other heart problems.
- You have low blood pressure, especially due to a low amount of fluid in the circulation.
- You have liver or kidney problems, as these organs have an effect on the way in which your system breaks down the medicine.
- You are suffering from oral mucositis
- You take antidepressants or antipsychotics, please refer to the section 'Other medicines and Breakyl'

For more information see section 3.

Consult your doctor while using Breakyl, if
- 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. Together 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.
- You have ever developed adrenal insufficiency or lack of sex hormones (androgen deficiency) with opioid use.

Children and adolescents
Do not give this medicine to children between the ages of 0 and 18 years.

Breakyl contains fentanyl in an amount which can be fatal to a child. Therefore, Breakyl must be kept out of sight and reach of children at all times.
If you are an athlete, be aware that this product may produce a positive reaction in anti-doping tests.

Other medicines and Breakyl

Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines, including medicines obtained without a prescription.

Do <u>not</u> use Breakyl if you are currently taking monoamine-oxidase (MAO) inhibitors (used for severe depression) or have done so in the past 2 weeks.

If you are taking any of the following talk to your doctor or pharmacist before starting Breakyl:
Any medicine which might normally make you tired or sleepy, e.g.:
- sleeping pills,
- medicines to treat anxiety, nervousness, depression,
- medicines to treat tense or rigid muscle (muscle relaxants),
- medicines to treat allergies (antihistamines).

Medicines that might interfere with the way, by which (the CYP3A4 isoenzyme in) your body breaks down Breakyl as these may increase the blood levels of fentanyl. This may result in increased or prolonged effects of Breakyl and may cause potentially fatal breathing problems. Such medicines are, e.g.:

- medicines for the treatment of bacterial infections (such as erythromycin, clarithromycin, telithromycin)
- medicines for the treatment of fungal infections (such as ketoconazole, itraconazole, fluconazole)
- medicines to control viral infections, i.e. HIV infections (such as ritonavir, indinavir, nelfinavir, saquinavir)
- medicines for the treatment of cardiovascular diseases (such as diltiazem, verapamil)
- medicines against severe nausea (such as aprepitant, dronabinol)
- medicines for the treatment of depressions (such as fluoxetine)
- medicines which inhibit gastric acid production (such as cimetidine)

The risk of side effects increases if you are taking medicines such as certain antidepressants or psychotics. Breakyl may interact with these medicines and you may experience mental status changes (e.g. agitation, hallucinations, coma), and other effects such as body temperature above 38°C, increase in heart rate, unstable blood pressure, and exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Your doctor will tell you whether Breakyl is suitable for you.

Medicines that may enhance the way, by which (the CYP3A4 isoenzyme in) your body breaks down fentanyl, thus decreasing the efficacy of Breakyl such as:
- sleeping pills or sedatives (such as phenobarbital)
- medicines to control epileptic convolutions/seizures (such as carbamazepine, phenytoin, oxcarbazepine)
- medicines to control viral proliferation (such as efavirenz, nevirapine)
- anti-inflammatory or immunosuppressive medicines (such as glucocorticoids)
- medicines for the treatment of diabetes (such as pioglitazone)
- antibiotics for treatment of tuberculosis (such as rifabutin, rifampicin)
- psycho-stimulating medicines (such as modafinil)
- medicines for the treatment of depressions (such as St. John's wort)

If you *stop* therapy with, or *decrease* the dose of, such active substances while using Breakyl, talk to your doctor. Your doctor will carefully monitor you for signs of opioid toxicity, and may adjust the dose of Breakyl accordingly.

Simultaneous use of Breakyl and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Therefore, simultaneous use should be avoided if other treatment options are possible.
However, if Breakyl is prescribed together with sedative medicines, the dose and duration should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking, and follow your doctor’s dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact you doctor, when experiencing such symptoms.

If you simultaneously use certain types of strong pain-killers, called partial opioid agonists/antagonists e.g. buprenorphine, nalbuphine and pentazocine, you could experience opiate withdrawal symptoms (nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating) while using these medicines.

Using Breakyl with food, drink and alcohol

Avoid drinking alcohol, as alcohol may additionally sedate and depress your respiration. Do not drink grapefruit juice, as this may slow down the way your body breaks down fentanyl, which may result in increased or prolonged effects of Breakyl and may cause potentially fatal breathing problems.

Pregnancy, breast-feeding and fertiliy

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breakyl should not be used during pregnancy unless you have discussed this with your doctor. You should not use Breakyl during childbirth because fentanyl may cause respiratory depression in the new-born child.

Fentanyl can get into breast milk and may cause side effects in the breast-fed infant. Do not use Breakyl if you are breast-feeding. You should not start breast-feeding until at least 5 days after the last dose of Breakyl.

Driving and using machines

Please ask your doctor whether you may safely drive a car, or operate machinery a few hours after taking Breakyl.

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

Breakyl contains propylene glycol (E1520), sodium benzoate (E211), methyl-parahydroxybenzoate (E218), and propyl-parahydroxybenzoate (E216).

Sodium benzoate is mildly irritant to the skin, eyes and mucous membranes. Methyl-parahydroxybenzoate and propyl-parahydroxybenzoate may cause allergic reactions (possibly delayed). Propylene glycol may cause skin irritation. This medicine contains less than 1 mmol sodium (23 mg) per buccal film, that is to say it is essentially 'sodium-free'.

3. HOW TO USE BREAKYL

Always use Breakyl exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosage

When you start using Breakyl your doctor will work with you to find the dose that will relieve your breakthrough pain (dose titration). This is necessary because your individual successful dose of Breakyl can not be predicted from the daily dose of opioids you are taking for treatment of your chronic cancer pain, or from other medicines which you may have taken for treatment of breakthrough cancer pain.

For dose titration your dose is gradually increased. When you have reached a dose, which provides you with adequate pain relief within 30 minutes and if any possibly occurring side effects are acceptable for you, you have identified the successful dose. It is important that you follow strictly the advice of your doctor.

Usually, the following procedure will be used for the *Dose Titration*.

Dose titration

You should start with the initial dose of 200 micrograms of Breakyl.
Contact your doctor, if your breakthrough pain is not relieved within 30 minutes after application of the Breakyl dose. If you have tolerated the dose, your doctor will advise you to take the next higher Breakyl dose for a subsequent breakthrough pain episode. Your doctor may gradually increase the dose from 200 to 400 and 600 micrograms up to 800 micrograms.

For this purpose Breakyl Start contains one unit of each strength: 200, 400, 600, and 800 micrograms.

By applying a combination of Breakyl 200 microgram buccal films simultaneously, these higher doses may be achieved:

1 buccal film Breakyl 200 equals a dose of 200 micrograms
2 buccal films Breakyl 200 equal a dose of 400 micrograms
3 buccal films Breakyl 200 equal a dose of 600 micrograms
4 buccal films Breakyl 200 equal a dose of 800 micrograms

In case the highest strength in Breakyl Start (800 micrograms) or the combination of 4 buccal films at one time (800 micrograms) is not sufficient for pain relief, your doctor may prescribe Breakyl 1200 micrograms for you. This is the highest available strength of Breakyl.

When you have identified the successful dose, your doctor will provide you with a prescription for this dose to treat subsequent breakthrough pain episodes by using this identified dose.

Breakyl should only be used once per breakthrough pain episode and you should wait for at least 4 hours before using the next Breakyl dose.

If you do not achieve adequate pain relief within 30 minutes after application of a Breakyl dose, you may use another rescue medication for breakthrough pain, if your doctor told you so.

Frequency of administration

You should not take more than four Breakyl doses per day.

Dose Readjustment

You must inform your doctor immediately if you are experiencing more than four breakthrough pain episodes per day. Your doctor may wish to increase the dose of your medicine for your persistent cancer pain. When your persistent pain is controlled again, your doctor may need to adjust your dose of Breakyl. For best results, let your doctor know about your pain and how Breakyl is working for you so that the dose can be adjusted if needed.

Do not change the doses of Breakyl or of your regular opioid therapy on your own. Changes in dosage must be directed and monitored by your doctor.

Methods of administration

Breakyl buccal film is for oromucosal use. When you attach a Breakyl buccal film to the inside of your cheek, fentanyl is absorbed directly through the lining of your mouth, into the blood circulation.

• Open the Breakyl sachet immediately prior to use as indicated by the instructions on the sachet;
• Use your tongue to wet the inside of your cheek or rinse your mouth with water to moisten the area for placement of Breakyl;
• With dry hands, take the Breakyl buccal film between your forefinger and thumb with the pink side facing to the thumb (figure 1)
• Place the Breakyl buccal film inside your mouth, so that the pink side makes smooth contact with the inner lining of your cheek (figure 2);
• Press and hold it in place for a minimum of 5 seconds until it sticks firmly. Now the white side should be visible (figure 3).
• When applying more than one Breakyl buccal film at the same time, make sure each film sticks directly to your oral mucosa. To avoid overlap, it is possible to apply films to both, left and right side of the buccal mucosa.

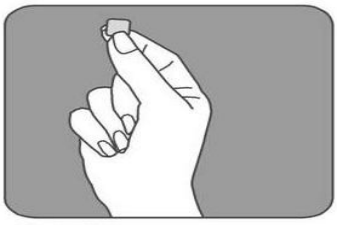


Figure 1

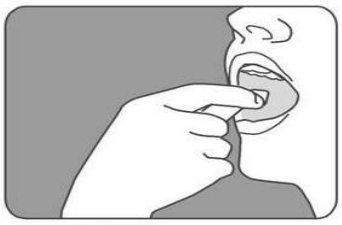


Figure 2


Figure 3

The Breakyl buccal film should stay in place on its own after this period. You may drink liquids after 5 minutes.
The buccal film will usually dissolve completely within 15 to 30 minutes after application. In individual cases complete dissolution may take more than 30 minutes, but this does not affect fentanyl absorption.

Avoid manipulating the buccal film with your tongue or fingers. You should not eat as long as the buccal film has not yet dissolved completely.
Do not chew or swallow Breakyl. If you do so, you will likely get less relief of your breakthrough pain.

If you use more Breakyl than you should or think someone has accidentally used Breakyl

If, after using Breakyl, you begin to feel very sleepy, remove the Breakyl buccal film or even parts of it from your mouth as quickly as possible and call another person to help you.
You or your caregiver should contact your doctor, hospital or emergency room for assessment of the risk and for advice, if you have taken more Breakyl than you should.

Symptoms of overdose may be:
- very sleepy
- dizzy
- feeling sick or vomiting
- very slow and/or shallow breathing
- or reduced body temperature, slow heart beat, difficulties coordinating arms and legs

If someone has accidentally taken Breakyl, they may have the same symptoms as described above for overdose.

At the beginning of treatment, these symptoms can occur, if your dose of Breakyl is too high or if you take too much Breakyl. You and your caregiver should discuss with your doctor how to take immediate action if this occurs.

***Note to caregivers*:**
If you see that the patient taking Breakyl or someone who has accidentally taken Breakyl for whom it is not prescribed, has slow and/or shallow breathing or if you have a hard time waking the person up, take the following steps immediately:
• In case the Breakyl buccal film is still sticking to the inner cheek of the patient, remove the buccal film or even parts of it from the individual's mouth as quickly as possible
• Call for emergency help
• While waiting for emergency help:
– If the person is asleep, awaken the person by calling her/his name and shaking her/his arm or shoulder
– If the person seems to be breathing slowly, prompt her/him to breathe every 5-10 seconds
– If the person has stopped breathing, give mouth to mouth resuscitation until help arrives

If you stop using Breakyl

You should discontinue Breakyl when you no longer have any breakthrough pain. You must however continue to take your usual opioid pain relieving medicine to treat your persistent cancer pain as advised by your doctor.
You may experience withdrawal symptoms similar to the possible side effects of Breakyl when discontinuing Breakyl. If you experience withdrawal symptoms or if you are concerned about your pain relief, you should contact your doctor. Your doctor will evaluate if you need medicine to reduce or eliminate the withdrawal symptoms.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Breakyl can cause side effects, although not everybody gets them.

The most serious side effects are shallow breathing, low blood pressure and shock. If you become very sleepy or have slow and/or shallow breathing, you or your caregiver should contact your doctor immediately and call for emergency help. If the buccal film is still in place in your cheek, it or even parts of it should be removed as quickly as possible.

The most frequent adverse reactions observed were nausea, somnolence, and dizziness.

Because patients using Breakyl are also taking regular opioid therapy such as morphine, oxycodone or transdermal fentanyl, for their persistent pain, opioid side effects may arise from either medication. Thus, it is not possible to definitively separate the effects of Breakyl from those of the other opioids.

The adverse events considered to be at least possibly-related to treatment, were as follows:

Common (may affect up to 1 in 10 people)**:**
- excessive tiredness/sleepiness, dizziness, headache, sedation
- sight problems (e.g. blurred or double vision)
- nausea/feeling sick, constipation, vomiting, dry mouth
- itching of the skin
- fatigue
- confusion

Uncommon (may affect up to 1 in 100 people)**:**
- blood pressure increased
- taste alteration, inactivity, memory difficulties, disturbance in thinking
- slow or shallow breathing, sinus congestion
- diarrhoea, oral mucosal inflammation, gum bleeding, indigestion, mouth ulcers, oral pain, painful swallowing
- unintentional loss of urine
- increased sweating, tendency to bruise
- muscle twitching, muscular weakness, pain in joints, muscular pain, pain in extremity, pain in jaw
- decreased appetite
- accidental injury (for example, falls)
- flushing/feeling hot
- weakness, chills, fever, thirst
- feeling anxious or nervous, hallucinations, delusion, abnormal dreams, sleeplessness (insomnia), restlessness

Very rare (may affect up to 1 in 10,000 people)**:**

- muscle jerks, convulsion ~~(fits)~~, abnormal sensations like tingling, numbness, increased touchiness also around the mouth, difficulty coordinating movements
- severe breathing difficulties
- abdominal pain, wind, abdominal bloating
- difficulty passing urine
- skin rash
- vasodilatation
- general feeling unwell
- swelling of arms or legs
- abnormal thinking, feeling detached, depression, mood swings, excessive feeling of well-being

Frequency not known (frequency cannot be estimated from the available data):

- delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares)
- withdrawal syndrome (may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating)

- drug dependence (addiction)
- drug abuse

There is a risk of abuse or addiction with Breakyl. The risk is higher if you have ever been addicted to or abused other medicines, street drugs, or alcohol.
Prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which can be life-threatening (see section 2).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE BREAKYL

Keep Breakyl out of the sight and reach of children at all times. The amount of fentanyl contained in Breakyl can be fatal to a child or a person, who does not use regular opioid therapy. Breakyl should be kept in a safe locked storage place.

Do not use Breakyl after the expiry date which is stated on the carton and each sachet as {MM.YYYY}. The expiry date refers to the last day of that month.

Do not store above 30ºC.

Do not refrigerate.

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

Do not use if the sachet has been damaged before opening. If a buccal film is damaged or cut during removal, it should not be used.

Do not throw away Breakyl via wastewater or household waste. If you are no longer using Breakyl, or if you have left over sachets in your home, ask your pharmacist how to dispose of these medicines no longer required. These measures will help to protect the environment and to avoid that unused medication is taken by children and/or persons, for whom it is not prescribed.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Breakyl contains

The active substance is fentanyl.

Breakyl 200 microgram buccal film
One buccal film contains 200 micrograms fentanyl (as fentanyl citrate),

Breakyl 400 microgram buccal film
One buccal film contains 400 micrograms fentanyl (as fentanyl citrate),

Breakyl 600 microgram buccal film
One buccal film contains 600 micrograms fentanyl (as fentanyl citrate),

Breakyl 800 microgram buccal film
One buccal film contains 800 micrograms fentanyl (as fentanyl citrate), or

Breakyl 1200 microgram buccal film
One buccal film contains 1200 micrograms fentanyl (as fentanyl citrate)

The other ingredients are
Active layer:
Propylene glycol (E1520),
sodium benzoate (E211),
methyl-parahydroxybenzoate (E218),
propyl-parahydroxybenzoate (E216),
ferric oxide (red) (E172),
anhydrous citric acid,
all-*rac*-alpha-tocopheryl acetate,
monobasic sodium phosphate (anhydrous),
sodium hydroxide,
Tribasic sodium phosphate (anhydrous),
polycarbophil,
hydroxypropyl cellulose,
hydroxyethyl cellulose,
Carmellose sodium.

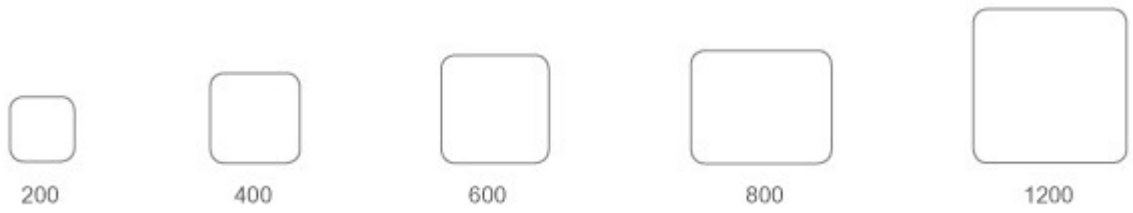
Backing layer:
sodium benzoate (E211),
methyl-parahydroxybenzoate (E218),
propyl-parahydroxybenzoate (E216),
anhydrous citric acid,
all-*rac*-alpha-tocopheryl acetate,
hydroxypropyl cellulose,
hydroxyethyl cellulose,
titanium dioxide (E171),
saccharin sodium,
peppermint oil.

This medicine contains, depending on strength, a maximum of 0.69 mg sodium benzoate in each dosage unit (see section 2) and less than 1 mmol sodium (23 mg) per buccal film, that is to say it is essentially 'sodium-free'.

What Breakyl looks like and contents of the pack

Breakyl is a soluble rectangular, flat, flexible buccal film with a pink side and a white side designed to deliver fentanyl directly into the blood circulation. The pink side contains the active substance fentanyl. The white side minimises fentanyl release into the saliva to avoid swallowing of the active substance.

The following stencil shows the sizes of the available Breakyl strengths:



Microgram microgram microgram microgram microgram

Each buccal film is individually sealed in a child-resistant sachet.

Breakyl is available in the following presentations:

Breakyl 200 microgram: cartons with 4, 10 or 28 sachets with one buccal film each.
Breakyl 400 microgram: cartons with 4, 10 or 28 sachets with one buccal film each.
Breakyl 600 microgram: cartons with 4, 10 or 28 sachets with one buccal film each.
Breakyl 800 microgram: cartons with 4, 10 or 28 sachets with one buccal film each.
Breakyl 1200 microgram: cartons with 4, 10 or 28 sachets with one buccal film each.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Mylan IRE Healthcare Limited,
Unit 35/36 Grange Parade,
Baldoyle Industrial Estate,
Dublin 12,
Ireland

Manufacturer
MEDA Pharma GmbH & Co. KG
Benzstr. 1
D-61352 Bad Homburg
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Norway: Buquel / Buquel Start
Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden, United Kingdom: Breakyl / Breakyl Start

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