PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Actiq® 200 mcg
Actiq® 400 mcg
Actiq® 600 mcg
Actiq® 800 mcg
Actiq® 1200 mcg
Actiq® 1600 mcg

Compressed tablets on a handle for oral transmucosal administration

Composition: Each compressed tablet on a handle contains:
Actiq 200 mcg: Fentanyl (as citrate) 200 mcg
Actiq 400 mcg: Fentanyl (as citrate) 400 mcg
Actiq 600 mcg: Fentanyl (as citrate) 600 mcg
Actiq 800 mcg: Fentanyl (as citrate) 800 mcg
Actiq 1200 mcg: Fentanyl (as citrate) 1200 mcg
Actiq 1600 mcg: Fentanyl (as citrate) 1600 mcg

For information on inactive and allergenic ingredients, see section 2 "Important information about some of the ingredients of the medicine" and section 6 – "Further Information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

This medicine is not intended for use in children and adolescents under 16 years of age.

Medicines from the opioid group may cause addiction, especially with prolonged use, and have the potential of misuse and overdose. An overdose reaction can be manifested by slow breathing and even cause death. Make sure that you are familiar with the name of the medicine, the dosage you take, the frequency of administration, the duration of treatment, side effects and potential risks. Additional information about 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
Taking this medicine with benzodiazepines, other central nervous system depressants (including drugs) or alcohol, may cause a sensation of severe sleepiness, breathing difficulties (respiratory depression), coma and death.

1. WHAT IS THE MEDICINE INTENDED FOR?

Actiq is intended for the treatment of breakthrough pain in adult and adolescent cancer patients, from the age of 16 and above, who are already taking other opioid medicines to relieve persistent pain and whose body has gotten used to treatment (opioid tolerance).

Therapeutic group
Opioid analgesic (narcotics).

Breakthrough pain is additional sudden pain, that occurs suddenly, despite taking your usual pain killer medicines.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:
- You do not regularly use the opioid medicine prescribed for you (e.g., codeine, fentanyl, hydromorphone, morphine, oxycodone, pethidine), every day on a regular schedule, for at least a week, to relieve persistent pain. If you have not been using these medicines, **do not take Actiq**, because it may increase the risk of your breathing becoming dangerously slow and/or shallow, or even to cessation of breathing.
- You are sensitive (allergic) to fentanyl or to any of the additional ingredients contained in the medicine (described in section 6).
- You are taking monoamine oxidase inhibitors (MAOIs) (medicines for treatment of severe depression) or took them in the past two weeks (see section 2 under "Before treatment with Actiq, tell the doctor if").
- You have severe breathing problems or severe lung problems, accompanied by pulmonary obstruction.
- You suffer from short-term pain (e.g., pain due to injuries, surgery, headaches or migraine), other than breakthrough pain.

Do not use Actiq if any of the above-listed conditions apply to you. If you are uncertain, consult your doctor or pharmacist before using Actiq.

Special warnings regarding use of the medicine
During the course of treatment with Actiq, continue using an opioid medicine, for relief of the persistent cancer pain.
Repeated use of Actiq may result in the medicine being less effective (you become accustomed to it) or make you dependent on it. Your doctor will monitor you for signs of these conditions.

Before treatment with Actiq, tell the doctor if:
- You still are not stabilized with the other opioid medicine for the relief of persistent (around-the-clock) cancer pain.
- You are sick with a disease that affects your breathing (e.g., asthma, wheezing, or shortness of breath).
- You are suffering from a head injury or any loss of consciousness.
- You have heart problems, especially a slow heart rate.
- You have liver or kidney problems – this will affect the way the medicine is broken down in your body.
- You have low blood pressure as a result of a low amount of fluids in the blood system.
- You have diabetes.
- You are over the age of 65 – you may need a lower dosage. Any dosage increase will be reviewed very carefully by your doctor.
- You are taking a benzodiazepine (see section 2 under "Drug interactions"). Use of benzodiazepines may increase the risk of serious side effects including death.
- You use antidepressants or antipsychotics (selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors [MAOIs]; see section 2 under "Do not use the medicine if" and under "Drug interactions"). Use of these medicines together with Actiq **can lead to a potentially life-threatening condition called "serotonin syndrome"** (see section 2 under "Drug interactions").
- You have ever abused or been dependent on opioids or any other drug, alcohol or illegal drugs.
- You have ever developed, during the course of opioid use, adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones, or lack of sex hormone (androgen deficiency) (see section 4 under "Severe side effects").
- You consume alcohol; please see section "Use of the medicine and alcohol consumption".

During treatment with Actiq, consult the doctor if:
- You experience pain or increased sensitivity to pain (hyperalgesia) which does not respond to a higher dosage of the medicine as prescribed by your doctor.
- You have signs of tooth decay. Actiq contains approximately 2 grams of sugar; frequent use may increase the risk of tooth decay that may be serious. It is important to take good care of your teeth during treatment with Actiq.
- You experience a combination of the following symptoms: nausea, vomiting, lack of appetite, fatigue, weakness, dizziness and low blood pressure. The appearance of these symptoms together may indicate a potentially life-threatening condition called adrenal insufficiency – in this condition the adrenal glands do not produce enough hormones.
- You experience trouble breathing during sleep (apnea - paused breathing).

Seek urgent medical assistance if:
- You experience symptoms such as difficulty in breathing or dizziness, swelling of the tongue, lips or throat while using Actiq. These might be early symptoms of serious allergic reactions (anaphylaxis/hypersensitivity, see section 4 under "Severe side effects").

Children and adolescents
Actiq is not intended for children and adolescents below 16 years of age.

Drug interactions
Do not use this medicine and tell the doctor or pharmacist if:
- You are taking other fentanyl preparations that have been prescribed for you in the past for breakthrough pain. If you still have some of these fentanyl preparations in your home, consult the pharmacist about how to dispose of them.
- You are taking monoamine oxidase inhibitors (MAOIs) (medicines for severe depression) or have taken them in the past two weeks (see section 2 under "Do not use the medicine if" and under "Before treatment with Actiq, tell the doctor if").

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:
- Sedative medicines such as benzodiazepines or similar medicines – concomitant use with Actiq increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Therefore, concomitant use should only be considered when other treatment options are not possible.
  If your doctor decides on combination treatment, the dosage and duration of treatment will be limited by your doctor.
  Tell the doctor about all sedative medicines that you are taking (such as sleeping pills, medicines to treat anxiety, some medicines to treat allergic reactions (antihistamines), or other tranquillizers); follow the doctor's instructions carefully. It is recommended that you explain to your friends and relatives how to identify the signs and symptoms described above. Contact your doctor when experiencing such symptoms.
- Some muscle relaxants, such as baclofen, diazepam (see also "Special warnings regarding use of the medicine").
- Medicines that might affect how your body breaks down Actiq – such as ritonavir or other medicines that help control HIV infection, other medicines known as 'CYP3A4 inhibitors' such as ketoconazole, itraconazole, or fluconazole (used to treat fungal infections), troleandomycin, clarithromycin, or erythromycin (medicines for bacterial infections) and medicines known as 'CYP3A4 inducers' such as rifampicin, or rifabutin (medicines for bacterial infections), carbamazepine, phenobarbital, or phenytoin (medicines used to treat convulsions).
- Certain types of strong pain killers, called partial agonist/antagonists e.g., buprenorphine, nalbuphine and pentazocine (medicines for treatment of pain). You may experience withdrawal syndrome (nausea, vomiting, diarrhea, anxiety, chills, tremor and sweating) while using these medicines.
- Serotonergic medicinal preparations used to treat depression (antidepressants, such as: selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs] or antipsychotics). Use of these medicines together with Actiq can lead to a potentially life-threatening condition called "serotonin syndrome" (see section 2 under "Before treatment with Actiq, tell the doctor if" and "Do not use the medicine if"). The symptoms of serotonin syndrome can include mental status changes (e.g., agitation, hallucinations and coma), and other effects such as body temperature above 38ºC, increased heart rate, unstable blood pressure, exaggeration of reflexes, muscular rigidity, lack of coordination and/or gastrointestinal effects (e.g., nausea, vomiting, diarrhea). The doctor will determine whether Actiq is suitable for you.

If you are due to have surgery requiring a general anesthetic, consult the doctor.

Use of the medicine and food and drink
- Actiq can be taken before or after meals, although it should not be used during the meals.
- You may drink some water before using Actiq to moisten the mouth, but do not drink or eat anything while using Actiq.
- Do not drink grapefruit juice while using Actiq, since it may affect the breakdown of the medicine in the body.

Use of the medicine and alcohol consumption
- Do not consume alcohol while using Actiq. This may increase the frequency of severe side effects, including death.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning a pregnancy, consult the doctor before using the medicine.
Pregnancy
Do not use the medicine during pregnancy unless so instructed by your doctor. If Actiq is used for a prolonged time during pregnancy, there is a risk of the newborn child having withdrawal symptoms which might be life-threatening if not identified and treated by the doctor (see section 4 under "Side effects of unknown frequency").
Do not use Actiq during child-birth since fentanyl may cause breathing difficulties in the newborn child.
Breastfeeding
Fentanyl can be secreted into breast milk and may cause side effects in a breastfeeding baby. Do not use Actiq if you are breastfeeding. Do not start breastfeeding for at least 5 days after the last dose of Actiq.

Driving and operating machinery
The medicine may affect your ability to drive or operate tools or machinery. Consult a doctor whether it is safe for you to drive or operate tools or machinery during the first few hours after using Actiq. Do not drive or operate machinery if: you feel sleepy or dizzy, you have blurred or double vision or if you have difficulty concentrating.
It is important that you know how you react to Actiq before driving or operating tools or machinery.

Important information about some of the ingredients of the medicine
- Actiq contains sucrose and lactose. If your doctor told you that you have an intolerance to certain types of sugar, consult the doctor before using Actiq.
- Each tablet contains approximately 2 grams of glucose. If you have diabetes, you need to take this into consideration.
- The glucose in the tablet may damage the teeth. Brush your teeth regularly.
- This medicine contains less than 23 mg sodium per tablet and is therefore considered sodium-free.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions.
The dosage and treatment regimen will be determined by the doctor only.
Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.

Do not exceed the recommended dose.
When you first start using Actiq, the doctor will determine, together with you, the appropriate dosage to relieve the breakthrough pain. It is very important that you use Actiq exactly as your doctor instructed you to.
- Do not change the dosages of Actiq or of other pain medicines on your own. A dosage change must be prescribed and assessed by the doctor.
- If you are uncertain about the correct dose, or if you have questions regarding use of the medicine, refer to a doctor.

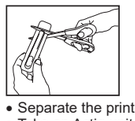
How the medicine is absorbed in your body
When you put the tablet in your mouth:
- The tablet dissolves and the active ingredient is released. The process takes approximately 15 minutes.
- The active ingredient is absorbed through the oral mucosa into the blood circulation.

Using the medicine this way enables rapid absorption, namely, the medicine will rapidly relieve the breakthrough pain.

While adjusting the dosage
During the use of Actiq you should start to feel some relief quickly. However, during the dose adjustment that controls the breakthrough pain, you may not feel sufficient pain relief 30 minutes after you start using one Actiq unit (15 minutes after completing use of an Actiq unit). In such a case, the doctor may allow you to take a second Actiq unit of the same strength for that same breakthrough pain episode. Do not use a second unit unless instructed to do so by the doctor. Never use more than two units to treat a single episode of breakthrough pain.
While adjusting the dosage, you may need to keep more than one strength of Actiq units at home. However, only Actiq units at the strength you need should be kept, in order to prevent possible confusion or overdose. Consult a pharmacist on how to dispose of the units you do not need.

How many units should be used
Once the adjusted dose has been found together with your doctor, use one unit for an episode of breakthrough pain.
Refer to the doctor if the adjusted dosage of Actiq does not relieve your breakthrough pain after a few consecutive episodes of breakthrough pain. The doctor will decide if it is necessary to change the dosage.
Tell the doctor immediately if you use Actiq more than 4 times a day, since there may be a need to change your treatment regimen. The doctor may change the treatment for your persistent pain; when your persistent pain is under control, the doctor will consider changing the Actiq dosage. If your doctor suspects that you developed Actiq-associated increased sensitivity to pain (hyperalgesia), he may consider lowering the dosage of Actiq (see section 2 under "Special warnings regarding use of the medicine"). To obtain optimal relief, tell the doctor about your pain and how Actiq affects you, so that the dosage can be changed if necessary.

How should this medicine be used?
Opening the package – Each Actiq unit is sealed in a separate blister package.
- Open the blister package when you are ready to use Actiq. Do not open it in advance.
- Hold the blister package with the printed side far away from you.
- Hold the short edge of the blister package.
- Place the scissors close to the end of the Actiq unit and cut the long tab end completely off (as shown).



- Separate the printed side from the blister package and peel it completely off of the tray.
- Take an Actiq unit out of the blister package and place it in your mouth immediately.

Using an Actiq unit
- Place the tablet between the cheek and the gums.
- Using the handle, turn the tablet in your oral cavity, especially along the cheeks. Twirl the handle often.

- To obtain maximal relief, finish the tablet within 15 minutes. If you finish too quickly, you will swallow more of the medicine and get less relief of the breakthrough pain.

- Do not bite or chew the tablet. This would mean lower levels in the blood and less relief of the pain as compared to use as per the instructions.
- If, for some reason, you do not complete the entire tablet each time you have breakthrough pain, tell your doctor.

How often should Actiq be used?
- After finding the dosage that effectively controls your pain, do not use more than 4 Actiq units per day. If you think you may need to use more than 4 Actiq units per day, tell the doctor immediately.

How many Actiq units to take
- Do not use more than two units to treat a single breakthrough pain episode.

If you accidentally took an overdose
The most common side effects resulting from overuse: feeling sleepy, nausea, or dizziness.
- If you start feeling dizzy, nauseous or very sleepy before the tablet has completely dissolved, take it out of your mouth and get help.

A severe side effect of Actiq is slow and/or shallow breathing. This can happen if your dose of Actiq is too high or if you took too much Actiq.
- If this happens, seek medical assistance immediately.

If a child or an adult accidentally took Actiq
If you think that someone accidentally used Actiq, call for medical assistance immediately. Try to keep the person alert (by calling his name and by shaking his hand or shoulder) until medical assistance arrives.

If you forgot to take the medicine
If you are still suffering from breakthrough pain, you can use Actiq as per your doctor's instructions. If the breakthrough pain has stopped, do not use Actiq until the next episode. Adhere to the treatment regimen as recommended by the doctor.

If you stop taking the medicine
Stop using Actiq when you no longer suffer from breakthrough pain. However, you must continue taking your regular opioid pain-killer medicine to treat your persistent cancer pain, as you have been instructed by your doctor. When discontinuing use of Actiq, you may experience withdrawal symptoms that are similar to the possible side effects of Actiq. If you experience withdrawal symptoms or if you are concerned about your pain relief, refer to your doctor.
The doctor will evaluate if you need medicine to reduce or eliminate the withdrawal symptoms.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Actiq may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Severe side effects
- The most severe side effects: shallow breathing, low blood pressure and shock.
  You or your caregiver should remove the Actiq unit from your mouth, contact the doctor, and immediately call for emergency medical assistance if you experience any of the following serious side effects – you may need urgent medical attention:
- You become very sleepy or experience slow and/or shallow breathing.
- Breathing difficulties or dizziness, swelling of the lips or tongue that may indicate early signs of a severe allergic reaction.

Note to caregivers
If you notice that the patient using Actiq is suffering from slow and/or shallow breathing, or if you have a hard time waking him up, take the following steps **immediately**:
- Using the handle, remove the Actiq unit from the patient's mouth and keep it out of the reach of children or pets until it is disposed of.
- **Call for emergency medical assistance.**
- When waiting for emergency medical assistance, if you notice that the patient is breathing slowly, instruct him to breath every 5-10 seconds.

If during use of Actiq, you feel very dizzy, sleepy or any other sick feeling, use the handle to remove the tablet and dispose of it according to the instructions in this leaflet (see section 5). Then, contact the doctor for further instructions on using Actiq.
- **Refer to a doctor if you experience a combination of the following symptoms:**
  Nausea, vomiting, loss of appetite, tiredness, weakness, dizziness and low blood pressure. Together, these symptoms may be indicative of a potentially life-threatening condition called adrenal insufficiency, a condition in which the adrenal glands do not produce enough hormones.
- Prolonged treatment with fentanyl during pregnancy may cause withdrawal symptoms in the newborn which can be life-threatening (see section 2 under "Pregnancy").

Additional side effects
Very common side effects (may affect more than 1 in 10 patients)
- Vomiting, nausea, constipation, abdominal pain.
- Weakness, sleepiness, dizziness, headaches.
- Shortness of breath.

Common side effects (may affect up to 1 in 10 patients)
- Confusion, anxiety, seeing or hearing things that do not exist (hallucinations), depression, mood swings.
- General unwell feeling.
- Muscle spasms, feeling of dizziness or "vertigo", loss of consciousness, sedation, tingling or numbness, coordination difficulties, increased or change in sensitivity to touch, convulsions.
- Dry mouth, mouth inflammation, tongue problems (for example, burning sensation or sores), taste alteration.
- Wind, abdominal bloating, indigestion, decreased appetite, weight loss.
- Blurred vision or double vision.
- Sweating, skin rash, skin irritation.
- Difficulty passing urine.
- Accidental injuries (for example: falls).

Uncommon side effects (may affect up to 1 in 100 patients)
- Tooth decay, paralysis of the gut, mouth sores, gum bleeding.
- Coma, stuttered speech.
- Strange dreams, feeling detached from reality, abnormal thoughts, excessive feeling of well being.
- Widening of blood vessels.
- Hives.

Side effects of unknown frequency
The following side effects have also been reported upon use of Actiq, but their frequencies are unknown:
- Receding gums, inflammation of the gums, tooth loss, severe breathing problems, flushing, feeling very warm, diarrhea, swelling of hands or legs, fatigue, insomnia, fever, withdrawal syndrome (can be manifested by onset of the following side effects: nausea, vomiting, diarrhea, anxiety, chills, tremor and sweating).
- Lack of sex hormones (androgen deficiency).
- Drug dependence (addiction).
- Drug abuse.
- Delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares).
- Trouble breathing during sleep

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

While using Actiq, you may experience irritation, pain and ulcer where the tablet is positioned, and bleeding from the gums.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?

- **The pain-relieving substance contained in Actiq is very strong and could be life-threatening if taken accidentally by a child.**
  Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (Exp. Date) that appears on the package. The expiry date refers to the last day of that month.
- **Store this medicine below 25°C.**
- Always keep Actiq in the tray package (blister), until the moment you are ready to use it. Do not use the medicine if the tray package is damaged or has been opened before you are ready to use it.
- If you are no longer using Actiq, or if you have Actiq units that were not used, return all the unused packages to the doctor or pharmacist.

How to dispose of Actiq after use
An Actiq tablet that was partially used can contain enough medicine to be harmful or life-threatening to a child. Even if there is little or no medicine left on the handle, you should be extra careful with the handle itself, as follows:
- If there is no more medicine on the handle, throw the handle away in a waste bin that is out of reach of children and pets.
- If there is medicine remaining on the handle, rinse the handle in hot running water to dissolve the remainder and then throw the handle away in a waste bin that is out of the reach of children and pets.
- If you did not finish the entire tablet and you cannot immediately dissolve the remaining medicine, keep the tablet out of the reach of children and pets until you can dispose of the partially used tablet, as detailed above.
- Do not flush a partly used tablet, handle or tray package down the toilet.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Inactive ingredients:
Tablet: hydrated dextrates, artificial berry flavor (maltodextrin, propylene glycol, artificial flavors and triethyl citrate), magnesium stearate, disodium phosphate, citric acid.
Edible glue: confectioner's sugar, modified maize based food starch E1450.
Holder: acrylonitrile/butadiene/styrene, terpolimer (ABS).
Imprinting ink: ethanol, deionised water, de-waxed white shellac, acetone, propylene glycol, brilliant blue FCF (E133), ammonium hydroxide (E527).

What the medicine looks like and the contents of the package
White to off-white cylindrical tablet, with "ACTIQ" and the tablet strength printed on it.
Each Actiq unit is attached to a handle and is packed in a tray. Each package contains 30 units.

License holder's name and address
Abic Marketing Ltd., P.O.B. 8077, Netanya.

Manufacturer's name and address
Cephalon Inc., Pennsylvania, USA.

This leaflet was revised in December 2020.

Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
Actiq 200 mcg: 138.21.31571
Actiq 400 mcg: 138.22.31572
Actiq 600 mcg: 138.23.31573
Actiq 800 mcg: 138.24.31574
Actiq 1200 mcg: 138.25.31575
Actiq 1600 mcg: 138.26.31576