

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Actiq 200 micrograms compressed lozenge with integral oromucosal applicator.
Actiq 400 micrograms compressed lozenge with integral oromucosal applicator.
Actiq 600 micrograms compressed lozenge with integral oromucosal applicator.
Actiq 800 micrograms compressed lozenge with integral oromucosal applicator.
Actiq 1200 micrograms compressed lozenge with integral oromucosal applicator.
Actiq 1600 micrograms compressed lozenge with integral oromucosal applicator.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One lozenge contains 200-400-600-800-1200-1600 micrograms fentanyl (as citrate).

Excipient(s):

Each lozenge contains dextrates (equivalent to approximately 2 grams of glucose), sucrose (approximately 30 milligrams confectioner's sugar) and propylene glycol (part of the artificial berry flavour and imprinting ink) as excipients.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Compressed lozenge with integral oromucosal applicator.

Actiq is formulated as a white to off-white compressed powder drug matrix attached using edible glue to a fracture resistant radio opaque plastic applicator, marked with the dosage strength.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Actiq is indicated for the management of breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain. Breakthrough pain is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain.

4.2 Posology and method of administration

In order to minimise the risks of opioid-related side-effects and to identify the "successful" dose, it is imperative that patients be monitored closely by health professionals during the titration process. Any unused Actiq units that the patient no longer requires must be disposed of properly. Patients must be reminded of the requirements to keep Actiq stored in a location away from children.

Method of administration

Actiq is intended for oromucosal administration, and therefore should be placed in the mouth against the cheek and should be moved around the mouth using the applicator, with the aim of maximising the amount of mucosal exposure to the product. The Actiq unit should be sucked, not chewed, as absorption of fentanyl via the buccal mucosa is rapid in comparison with systemic absorption via the gastrointestinal tract. Water may be used to moisten the buccal mucosa in patients with a dry mouth.

The Actiq unit should be consumed over a 15 minute period. If signs of excessive opioid effects appear before the Actiq unit is fully consumed it should be immediately removed, and consideration given to decreasing future dosages.

Dose titration and maintenance therapy

Actiq should be individually titrated to a “successful” dose that provides adequate analgesia and minimises side effects. In clinical trials the successful dose of Actiq for breakthrough pain was not predicted from the daily maintenance dose of opioid.

a) Titration

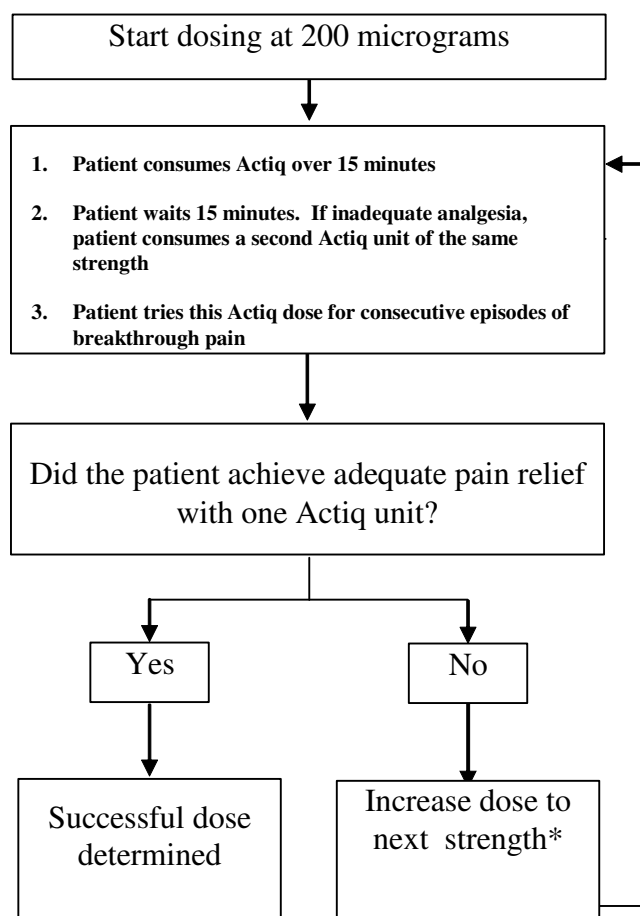
Before patients are titrated with Actiq, it is expected that their background persistent pain will be controlled by use of opioid therapy and that they are typically experiencing no more than 4 episodes of breakthrough pain per day.

The initial dose of Actiq used should be 200 micrograms, titrating upwards as necessary through the range of available dosage strengths (200, 400, 600, 800, 1200 and 1600 micrograms). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable side effects using a single dosage unit per episode of breakthrough pain. This is defined as the successful dose.

During titration, if adequate analgesia is not obtained within 15 minutes after the patient completes consumption of a single Actiq unit, a second Actiq unit of the same strength may be consumed. No more than two Actiq units should be used to treat any individual pain episode. At 1600micrograms, a second dose is only likely to be required by a minority of patients.

If treatment of consecutive breakthrough pain episodes requires more than one dosage unit per episode, an increase in dose to the next higher available strength should be considered.

Actiq[®] Titration Process



*Available dosage strengths include: 200, 400, 600, 800, 1200 and 1600 micrograms

Maintenance

Once a successful dose has been established (i.e., on average, an episode is effectively treated with a single unit), patients should be maintained on this dose and should limit consumption to a maximum of four Actiq units per day.

Patients should be monitored by a health professional to ensure that the maximum consumption of four units of Actiq per day is not exceeded.

Dose re-adjustment

If more than four episodes of breakthrough pain are experienced per day, over a period of more than four consecutive days the dose of the long acting opioid used for persistent pain should be re-evaluated. If the dose of the long acting opioid is increased, the dose of Actiq to treat breakthrough pain may need to be reviewed.

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

Discontinuation of therapy

Actiq therapy may usually be immediately discontinued if no longer required for breakthrough pain only, in patients who continue to take their chronic opioid therapy for persistent pain.

For patients requiring discontinuation of all opioid therapy, account should be taken of the Actiq dose in consideration of a gradual downward opioid titration to avoid the possibility of abrupt withdrawal effects.

Use in children

The appropriate posology and safety of Actiq have not been established in children and adolescents.

Use in the elderly

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously. Therefore dose titration needs to be approached with particular care. In the elderly, elimination of fentanyl is slower and the terminal elimination half-life is longer, which may result in accumulation of the active substance and to a greater risk of undesirable effects.

Formal clinical trials with Actiq have not been conducted in the elderly. It has been observed, however, in clinical trials that patients over 65 years of age required lower doses of Actiq for successful relief of breakthrough pain.

Use in special patient populations

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

4.3 Contraindications

Hypersensitivity to fentanyl or to any of the excipients.

Simultaneous use of monoamine-oxidase (MAO) inhibitors, or within 2 weeks after the cessation of the use of MAO inhibitors.

Severe respiratory depression or severe obstructive lung conditions.

4.4 Special warnings and precautions for use

It is important that the long acting opioid treatment used to treat the patient's persistent pain has been stabilised before Actiq therapy begins.

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

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

The product should not be given to opioid-naïve patients as there is an increased risk of respiratory depression and the appropriate dose in this patient population has not yet been determined.

Actiq should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure, or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

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

In addition, Actiq should be administered with caution to patients with liver or kidney dysfunction. The influence of liver and renal impairment on the pharmacokinetics of the medicinal product has not been evaluated, however, when administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal disease due to alterations in metabolic clearance and plasma proteins. After administration of Actiq, impaired liver and renal function may both increase the bioavailability of swallowed fentanyl and decrease its systemic clearance, which could lead to increased and prolonged opioid effects. Therefore, special care should be taken during the titration process in patients with moderate or severe hepatic or renal disease.

Careful consideration should be given to patients with hypovolaemia and hypotension.

Diabetic patients should be advised that the medicine product contains dextrates (dextrates are composed of 93% dextrose monohydrate and 7% maltodextrin. The total glucose load per dosage unit is approximately 1.89 grams per dose).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Normal oral hygiene is recommended to avoid any potential harm to the teeth

An evaluation of each out-patient concerning possible accidental child exposures should be undertaken.

Lozenges must be kept out of reach and sight of children and non-patients at all times before and after use. For instructions on handling and disposal, see Section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Fentanyl is metabolized by the CYP3A4 isoenzyme in the liver and intestinal mucosa. Potent inhibitors of CYP3A4 such as macrolide antibiotics (e.g. erythromycin), azole antifungals (e.g. ketoconazole, itraconazole, and fluconazole) and certain protease inhibitors (e.g. ritonavir), may increase the bioavailability of swallowed fentanyl and may also decrease its systemic clearance which may result in increased or prolonged opioid effects. Similar effects could be seen after concurrent ingestion of grapefruit juice, which is known to inhibit CYP3A4. Hence caution is advised if fentanyl is given concomitantly with CYP3A4 inhibitors.

The concomitant use of other CNS depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects.

Withdrawal symptoms may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, or mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, buprenorphine, nalbuphine).

4.6 Pregnancy and lactation

There are no adequate data from the use of fentanyl in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). Opioid analgesic agents can cause neonatal respiratory depression. With long-term use during pregnancy, there is a risk of neonatal withdrawal symptoms. Actiq should not be used in pregnancy unless clearly necessary.

It is advised not to use fentanyl during delivery because fentanyl passes through the placenta and may cause respiratory depression in the foetus. The placental transfer ratio is 0.44 (foetal:maternal ratio 1.00:2.27).

Fentanyl passes into breast milk, therefore women should not breast-feed while taking Actiq because of the possibility of sedation and/or respiratory depression in their infants. Breast feeding should not be restarted until at least 24 hours after the last administration of fentanyl.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, opioid analgesics may impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients should be advised not to drive or operate machinery if they experience somnolence, dizziness, blurred or double vision while taking Actiq.

4.8 Undesirable effects

Typical opioid side effects are to be expected with Actiq. Frequently, these will cease or decrease in intensity with continued use of the product, as the patient is titrated to the most appropriate dose. However, the most serious adverse events are respiratory depression (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension and shock and all patients should be closely monitored for these.

Application site reactions, including gum bleeding and irritation, have been reported in post-marketing use.

Because the clinical trials of Actiq were designed to evaluate safety and efficacy in treating breakthrough pain, all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent pain. Thus it is not possible to definitively separate the effects of Actiq alone.

The adverse events considered to be at least possibly-related to treatment, from clinical trials were as follows (very common >10%, common >1 - 10%, uncommon >0.1 - 1%):

Metabolism and nutrition disorders

Uncommon: anorexia

Psychiatric disorders

Common: confusion, anxiety, hallucinations, abnormal thinking

Uncommon: abnormal dreams, depersonalisation, depression, emotional lability, euphoria

Nervous system disorders

Very common: somnolence, dizziness

Common: headache, myoclonus, taste perversion

Uncommon: paraesthesia (including hyperaesthesia/circumoral paraesthesia), abnormal gait/incoordination

Eye disorders

Uncommon: abnormal vision (blurred, double vision)

Vascular disorders

Common: vasodilatation

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea

Gastrointestinal disorders

Very common: nausea, constipation

Common: vomiting, dry mouth, abdominal pain, dyspepsia, mouth ulcers/stomatitis, tongue disorder (for example, burning sensation, ulcers)

Uncommon: flatulence, abdomen enlarged

Skin and subcutaneous tissue disorders

Common: pruritus, sweating
Uncommon: rash

Renal and urinary disorders

Uncommon: urinary retention

General disorders and administration site conditions

Common: asthenia

Uncommon: malaise

Injury, poisoning and procedural complications

Common: accidental injury (for example, falls)

4.9 Overdose

The symptoms of fentanyl overdosage are expected to be similar in nature to those of intravenous fentanyl and other opioids, and are an extension of its pharmacological actions, with the most serious significant effect being respiratory depression.

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

For treatment of overdosage (accidental ingestion) in the opioid naïve person, intravenous access should be obtained, and naloxone or other opioid antagonists should be employed as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the Summary of Product Characteristics of the individual opioid antagonist for details about such use.

For treatment of overdose in opioid-maintained patients, intravenous access should be obtained. The judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid analgesic, phenylpiperidone derivative. ATC code N02A BO3.

Fentanyl, a pure opioid agonist, acts primarily through interaction with mu-opioid receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacological effect of the interaction of fentanyl with mu-opioid receptors is analgesia. The analgesic effects of fentanyl are related to the blood level of the active substance, if proper allowance is made for the delay into and out of the CNS (a process with a 3-5 minute half-life). In opioid-naïve individuals, analgesia occurs at blood levels of 1 to 2 ng/ml, while blood levels of 10-20 ng/ml would produce surgical anaesthesia and profound respiratory depression.

In patients with chronic cancer pain on stable doses of regularly scheduled opioids to control their persistent pain, Actiq produced significantly more breakthrough pain relief compared with placebo at 15, 30,

45, and 60 minutes following administration.

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

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

All opioid mu-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients with pain and those receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. In non-tolerant subjects, typically peak respiratory effects are seen 15 to 30 minutes following the administration of Actiq, and may persist for several hours.

5.2 Pharmacokinetic properties

General introduction

Fentanyl is highly lipophilic and can be absorbed very rapidly through the oral mucosa and more slowly by the conventional gastrointestinal route. It is subject to first-pass hepatic and intestinal metabolism and the metabolites do not contribute to fentanyl's therapeutic effects.

Absorption

The absorption pharmacokinetics of fentanyl from Actiq are a combination of rapid oromucosal absorption and slower gastrointestinal absorption of swallowed fentanyl. Approximately 25% of the total dose of Actiq is rapidly absorbed from the buccal mucosa. The remaining 75% of the dose is swallowed and slowly absorbed from the gastrointestinal tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Absolute bioavailability is about 50% compared to intravenous fentanyl, divided equally between rapid oromucosal and slower gastrointestinal absorption. C_{max} ranges from 0.39 to 2.51 ng/ml after consumption of Actiq (200 micrograms to 1600 micrograms). T_{max} is around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes).

Distribution

Animal data show that fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1- acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V_{ss}) is 4 l/kg.

Biotransformation

Fentanyl is metabolised in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. More than 90% of the administered dose of fentanyl is eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.

Elimination

Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the faeces. The metabolites are mainly excreted in the urine, while faecal excretion is less important. The total plasma clearance of fentanyl is 0.5 l/hr/kg (range 0.3-0.7 l/hr/kg). The terminal elimination half-life after Actiq administration is about 7 hours.

Linearity/non-linearity

Dose proportionality across the available range of dosages (200 micrograms to 1600 micrograms) of Actiq has been demonstrated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Studies with female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed. Teratogenic effects have not been demonstrated.

Long term carcinogenicity studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lozenge:

Dextrates hydrated (containing glucose)
Citric acid, anhydrous
Disodium phosphate, anhydrous
Artificial berry flavour (maltodextrin, propylene glycol, artificial flavours and triethylcitrate)
Magnesium stearate

Edible glue used to attach the lozenge to the handle:

Modified maize based food starch (E1450)
Confectioner's sugar (sucrose and maize starch)
Water, purified

Imprinting ink:

Ethanol
De-ionised water
De-waxed white shellac
Propylene glycol
Blue synthetic coal tar dye (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Each Actiq dosage unit is contained in a heat sealed blister package consisting of a paper/foil laminated lid, and a PVC/Aclar thermoformed blister, supplied in cartons of 3, 6, 15 or 30 individual units.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Patients and their carers must be instructed that Actiq contains an active substance in an amount that can be fatal to a child. Patients and their carers must be instructed to keep all units out of the reach and sight of children and to discard open units appropriately.

Lozenges with residual active substance should at no time be discarded or misplaced. Any used or unused but no longer required product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Cephalon UK Limited
1 Albany Place
Hyde Way
Welwyn Garden City
Hertfordshire
AL7 3BT
UK

8. MARKETING AUTHORISATION NUMBER(S)

Actiq 200 microgram compressed logenze with integral oromucosal applicator
PL 16260/003

Actiq 400 microgram compressed logenze with integral oromucosal applicator
PL 16260/004

Actiq 600 microgram compressed logenze with integral oromucosal applicator
PL 16260/005

Actiq 800 microgram compressed logenze with integral oromucosal applicator
PL 16260/006

Actiq 1200 microgram compressed logenze with integral oromucosal applicator
PL 16260/007

Actiq 1600 microgram compressed logenze with integral oromucosal applicator
PL 16260/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 10 August 2002

Date of renewal: 08 October 2005

10. DATE OF REVISION OF THE TEXT

July 2009