SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ACTIQ 1200 micrograms compressed lozenge with integral oromucosal applicator.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIQ 1,200 micrograms compressed lozenge with integral oromucosal applicator.
One lozenge contains 1200 micrograms fentanyl (as citrate).

Excipient with known effect:
One lozenge contains approximately 1.89 g glucose and 20-36 mg sucrose.

For the 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 medicinal product matrix attached using edible glue to a fracture resistant radio opaque plastic applicator. The dosage strength is marked on the lozenge and on the plastic applicator.

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.
Patients receiving maintenance opioid therapy are those who are taking at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

4.2 Posology and method of administration

Posology

In order to minimise the risks of opioid-related adverse reactions and to identify the "successful" dose, it is imperative that patients be monitored closely by health professionals during the titration process.
ACTIQ is not interchangeable on a mcg to mcg basis with other short-acting fentanyl products that are indicated for the use of breakthrough cancer pain, as the pharmacokinetic profiles and/or dosing schedules of these products are significantly different. Patients should be instructed not to use more than one short-acting fentanyl product concurrently for the treatment of breakthrough cancer pain, and to dispose of any fentanyl product prescribed for breakthrough pain (BTP) when switching to ACTIQ. The number of ACTIQ strengths available to the patient at any time should be minimised to prevent confusion and potential overdose.
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.

Adults

Dose titration and maintenance therapy
ACTIQ should be individually titrated to a "successful" dose that provides adequate analgesia and minimises

adverse reactions. In clinical trials the successful dose of ACTIQ for breakthrough pain was not predicted from the daily maintenance dose of opioid.

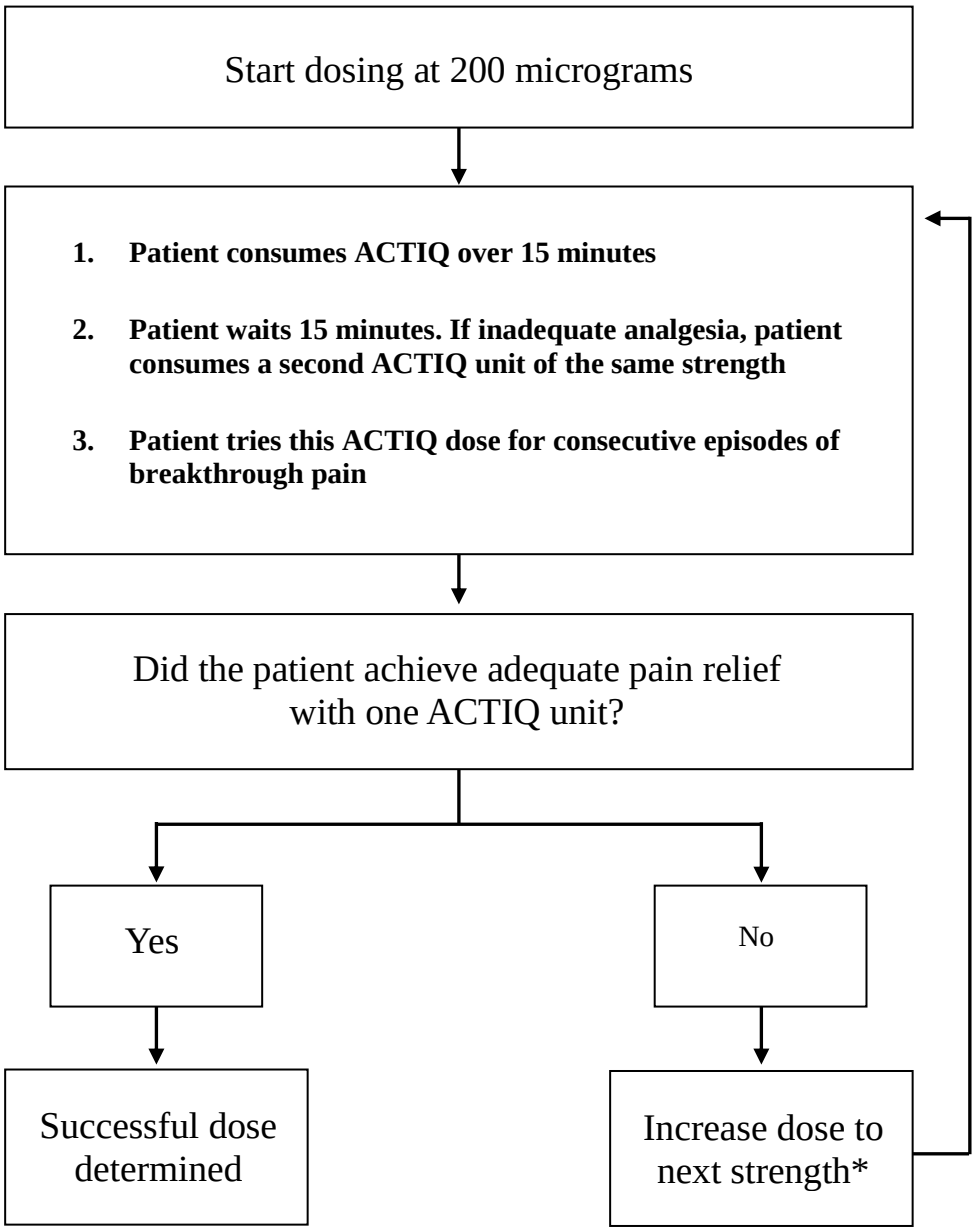
a) Titration
Before patients are titrated with ACTIQ, it is expected that their background persistent pain will be controlled by use of opioid therapy and that they are typically experiencing no more than 4 episodes of breakthrough pain per day.

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, 1,200 and 1,600 micrograms). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable adverse reactions 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 30 minutes after starting the first unit (i.e. 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 1600 micrograms, 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

b) 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
The maintenance dose of ACTIQ should be increased when an episode is not effectively treated with a single unit for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for dose titration (see above).

If more than four episodes of breakthrough pain are experienced per day the dose of the maintenance opioid therapy used for persistent pain should be re-evaluated. If the dose of the maintenance opioid therapy is

increased, the dose of ACTIQ to treat breakthrough pain may need to be reviewed.

In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

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

Treatment duration and goals
Before initiating treatment with ACTIQ, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4). ACTIQ should not be used longer than necessary.

Discontinuation of therapy
ACTIQ should be discontinued immediately if the patient no longer experiences breakthrough pain episodes. The treatment for the persistent background pain should be kept as prescribed. If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor as gradual downward opioid titration is necessary in order to avoid the possibility of abrupt withdrawal effects.

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 patients with hepatic or renal impairment

Special care should be taken during the titration process in patients with kidney or liver dysfunction (see section 4.4).

Paediatric population

Adolescents aged 16 years and above:
Follow adult dosage.

Children and adolescents below 16 years:
Safety and efficacy in children and adolescents below 16 years have not been established. There is limited clinical trial experience of the use of ACTIQ in paediatric patients already receiving maintenance opioid therapy (see sections 5.1 and 5.2). Use in this patient population is therefore not recommended.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients without maintenance opioid therapy as there is an increased risk of respiratory depression.
- Treatment of acute pain other than breakthrough pain.
- Simultaneous use of monoamine oxidase inhibitors (MAO inhibitors), or within 2 weeks after the cessation of the use of MAO inhibitors (see sections 4.4 and 4.5).
- Patients being treated with medicinal products containing sodium oxybate.
- Severe respiratory depression or severe obstructive lung conditions.

4.4 Special warnings and precautions for use

Because of the risks, including fatal outcome, associated with accidental exposure, misuse, and abuse, patients and their carers must be advised to keep ACTIQ in a safe and secure place, not accessible by others.

Accidental use in children

Patients and their carers must be instructed that ACTIQ contains an active substance in an amount that can be fatal to a child. Death has been reported in children who have accidentally ingested ACTIQ.
Patients and their carers must be instructed to keep all units out of the sight and reach of children and to discard open and unopened units appropriately. An evaluation of each out-patient concerning possible accidental child exposures should be undertaken.

Maintenance opioid therapy

The product must not be given to patients without maintenance opioid therapy as there is an increased risk of respiratory depression and death. It is important that the maintenance opioid therapy used to treat the patient's persistent pain has been stabilised before ACTIQ therapy begins and that the patient continues to be treated with the maintenance opioid therapy whilst using ACTIQ.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical dependence and psychological dependence may develop upon repeated administration of opioids. Fentanyl can be abused in a manner similar to other opioids and all patients treated with opioids require monitoring for signs of abuse and addiction. Patients at increased risk of opioid abuse may still be appropriately treated with opioids; however, these patients will require additional monitoring for signs of misuse, abuse or addiction.

Repeated use of ACTIQ may lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of ACTIQ may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with ACTIQ and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. Patients should be advised to contact their physician if these signs occur.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of fentanyl, the possibility of opioid-induced hyperalgesia should be considered. A fentanyl dose reduction or discontinuation of fentanyl treatment or treatment review may be indicated

Endocrine effects

Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decrease in plasma cortisol and testosterone. Clinical signs and symptoms may manifest from these hormonal changes.

Cases of adrenal insufficiency have been reported with opioid use including fentanyl lozenges, more often following greater than one month of use. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers (see section 4.8).

Respiratory depression

As with all opioids, there is a risk of clinically significant respiratory depression associated with the use of ACTIQ, patients should be monitored accordingly.
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.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Alcohol

The concomitant use of alcohol with fentanyl can produce increased depressant effects which may result in a fatal outcome (see section 4.5).

Risks of concomitant administration with benzodiazepines

Concomitant use of opioids, including ACTIQ, with benzodiazepines may result in profound sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of opioids and benzodiazepines should be made only in patients for whom alternative treatment options are inadequate.
If a decision is made to prescribe ACTIQ concomitantly with benzodiazepines, the lowest effective dosages and minimum durations of concomitant use should be chosen. Patients should be closely monitored for signs and symptoms of respiratory depression and sedation (see section 4.5).

Intracranial effects of CO_2 retention, impaired consciousness, head injury

ACTIQ should only be administered with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 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.

Bradyarrhythmias

Fentanyl may produce bradycardia. Fentanyl should be used with caution in patients with previous or pre-existing bradyarrhythmias.

Hepatic or renal impairment

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.

Hypovolaemia, hypotension

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

Dental decay

Normal oral hygiene is recommended to reduce any potential harm to the teeth. Because ACTIQ contains approximately 2 grams of sugar, frequent consumption increases the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medicinal products may add to this risk. During treatment with ACTIQ, regular dental visits are advised.

Serotonin syndrome

Caution is advised when ACTIQ is co-administered with medicinal products that affect the serotoninergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic medicinal products such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), and with medicinal products which impair metabolism of serotonin (including monoamine oxidase inhibitors [MAO inhibitors]) (see section 4.3). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, treatment with ACTIQ should be discontinued.

Anaphylaxis, hypersensitivity

Anaphylaxis and hypersensitivity have been reported in association with the use of oral transmucosal fentanyl products (see section 4.8).

Paediatric population

ACTIQ is not recommended for use in children and adolescents below 16 years due to lack of data on safety and efficacy (see sections 5.1 and 5.2).

Excipients

Glucose
Contains approximately 1.89 g glucose per dose. This should be taken into account in patients with diabetes mellitus.
Patients with rare glucose-galactose malabsorption should not take this medicinal product.
May be harmful to the teeth.

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.
May be harmful to the teeth.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per lozenge, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that affect CYP3A4 activity

CYP3A4 inhibitors
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.

CYP3A4 inducers
Co-administration with agents that induce 3A4 activity may reduce the efficacy of ACTIQ.

Agents that can increase CNS depressant effects

Co-administration of fentanyl with other CNS depressants, including other opioids, sedatives or hypnotics (including benzodiazepines), general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines, gabapentinoids (gabapentin and pregabalin) and alcohol can produce additive depressant effects which may result in respiratory depression, hypotension, profound sedation, coma or a fatal outcome (see section 4.4).

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Partial opioid agonists/antagonists

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

Serotonergic agents

Co-administration of fentanyl with a serotonergic agent, such as a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) or a monoamine oxidase inhibitor (MAO inhibitor), may increase the risk of serotonin syndrome, a potentially life-threatening condition(see section 4.3).

Sodium oxybate

Concomitant use of medicinal products containing sodium oxybate and fentanyl is contraindicated (see section 4.3). The treatment of sodium oxybate should be discontinued before start of treatment with ACTIQ.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of 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 opioid withdrawal syndrome which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. ACTIQ should not be used in pregnancy unless clearly necessary.
If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see section 4.8).

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

Breastfeeding

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breastfed child. Fentanyl should not be used by breastfeeding women and breast feeding should not be restarted until at least 5 days after the last administration of fentanyl.

Fertility

There are no human data on fertility available. In animal studies, male fertility was impaired (see section 5.3).

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 using ACTIQ.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

The medicine is likely to affect your ability to drive,
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely.

4.8 Undesirable effects

Typical opioid adverse reactions 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, irritation, pain and ulcer 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 following adverse reactions have been reported with ACTIQ and/or other fentanyl-containing compounds during clinical studies and post marketing experience. Adverse reactions are listed below as MedDRA preferred term by system organ class and frequency (frequencies are defined as: very common ≥ 1/10, common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100, not known (cannot be estimated from the available data):

System organ class	**Very common**	**common**	**uncommon**	**Not known**
Immune system disorders				anaphylactic reaction, tongue oedema, lip oedema
Endocrine disorders				adrenal insufficiency, androgen deficiency
Metabolism and nutrition disorders		anorexia		
Psychiatric disorders		confusion, anxiety, hallucinations, depression, emotional lability	abnormal dreams, depersonalisation, abnormal thinking, euphoria	Insomnia, drug dependence (addiction), drug abuse (see section 4.4), delirium
Nervous system disorders	somnolence, dizziness, headache	loss of consciousness, convulsion, vertigo, myoclonus, sedation, paraesthesia (including hyperaesthesia/circumoral paraesthesia), abnormal gait/incoordination, taste perversion	coma, slurred speech	
Eye disorders		abnormal vision (blurred, double vision)		
Vascular disorders			vasodilatation	flushing, hot flush
Respiratory, thoracic and mediastinal disorders	dyspnoea			pharyngeal oedema, respiratory depression, sleep apnoea syndrome
Gastrointestinal disorders	nausea, vomiting, constipation,	dry mouth, dyspepsia, stomatitis,	ileus, mouth ulcers, dental caries,	tooth loss, gingival recession,

System organ class	Very common	common	uncommon	Not known
	abdominal pain	tongue disorder (for example, burning sensation, ulcers), flatulence, abdomen enlarged	gingival bleeding	gingivitis, diarrhoea
Skin and subcutaneous tissue disorders		pruritus, sweating, rash	urticaria	
Renal and urinary disorders		urinary retention		
General disorders and administration site conditions	asthenia	application site reactions including irritation, pain and ulcer, malaise		fatigue, peripheral oedema, pyrexia, withdrawal syndrome*, neonatal withdrawal syndrome (see section 4.6), drug tolerance, bleeding at the site of application
Investigations		weight decreased		
Injury, poisoning and procedural complications		accidental injury (for example, falls)		

* opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating have been observed with transmucosal fentanyl.

Description of selected adverse reactions

Tolerance
Tolerance can develop on repeated use.

Drug dependence
Repeated use of ACTIQ can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

The symptoms of fentanyl overdose 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 effects being altered mental status, loss of consciousness, coma, cardiorespiratory arrest, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.
Cases of Cheyne-Stokes respiration have been observed in case of fentanyl overdose, particularly in patients with history of heart failure.
Toxic leukoencephalopathy has also been observed with fentanyl overdose.

Management

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.

Overdose (accidental ingestion) in the opioid naive person

For treatment of overdose (accidental ingestion) in the opioid naive 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.

Overdose in opioid-maintained patients
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: N02AB03.

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 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.

Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes (see also section 4.8).

Additional secondary pharmacological effect includes miosis.

Paediatric population
There is limited experience of the use of ACTIQ in paediatric patients, below the age of 16. In a clinical study, 15 (out of 38) paediatric patients, ranging in age from 5 to 15 years, already receiving maintenance opioid therapy and with breakthrough pain were treated with ACTIQ. The study was too small to allow conclusions on safety and efficacy in this patient population.

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 1,600 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 1,600 micrograms) of ACTIQ has been demonstrated.

Paediatric population
In a clinical study, 15 paediatric patients, ranging in age from 5 to 15 years, already receiving maintenance opioid therapy and with breakthrough pain were treated with ACTIQ at doses ranging from 200 mcg to 600 mcg. Area under the curve values based on observed concentrations were 2-fold higher in younger children than adolescents (5.25 *versus* 2.65 ng.hr/mL, respectively) and 4-fold higher in the younger children as compared to adults (5.25 *versus* 1.20 ng.hr/mL). On a weight-adjusted basis, clearance and volume of distribution values were similar across the age range.

5.3 Preclinical safety data

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

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is consistent with the sedative effects of fentanyl in animal studies.
In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) with fentanyl did not induce any findings indicative of oncogenic potential. Evaluation of brain slides from carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lozenge:

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

Edible glue used to attach the lozenge to the handle:

Modified maize based food starch (E 1450)
Confectioner’s sugar (containing sucrose and maize starch)
Water, purified

Imprinting ink:

De-ionised water
De-waxed white shellac
Blue synthetic coal tar dye (E 133)
Ammonium hydroxide (E 527) for pH adjustment

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30 °C.
Store in protective blister until ready for use.

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

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

Teva Pharma B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Actiq 1200 microgram compressed lozenge with integral oromucosal applicator
PL 14776/0096

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 October 2000
Date of latest renewal: 08 October 2010

10. DATE OF REVISION OF THE TEXT

23 May 2024