CLEAN

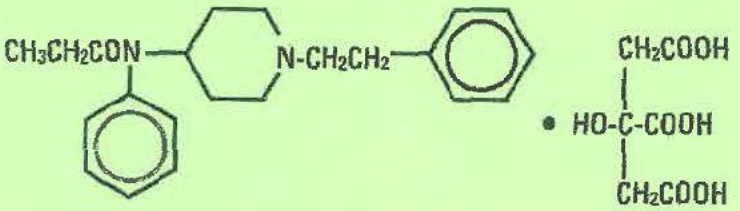
Document 7

PRODUCT INFORMATION

ACTIQ®
(fentanyl citrate)
200, 400, 600, 800, 1200 and 1600 micrograms
Lozenge with integral applicator

NAME OF THE MEDICINE

Fentanyl citrate.



DESCRIPTION

ACTIQ (fentanyl citrate) is a synthetic opioid analgesic related to pethidine and with similar properties to morphine. Fentanyl citrate is a white, crystalline powder with a molecular weight of 528.6 and the molecular formula $C_{22}H_{28}N_2O,C_6H_8O_7$. Its chemical name is N-(1-Phenethyl-4-piperidyl) propionanilide dihydrogen citrate. The CAS Registry Number for fentanyl citrate is 990-73-8.

The citrate salt is sparingly soluble to soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; soluble to freely soluble in methyl alcohol.

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. ACTIQ is available in six unit strengths of 200, 400, 600, 800, 1200 and 1600 micrograms of fentanyl base. Fentanyl citrate 157 µg is approximately equivalent to 100 µg of fentanyl.

The compressed powder dosage unit contains dextrates (93% dextrose monohydrate, as D-glucose, and 7% maltodextrin), anhydrous citric acid, anhydrous dibasic sodium phosphate, artificial berry flavour (maltodextrin, propylene glycol, artificial flavours, and triethyl citrate) and magnesium stearate.

The composition of the edible glue used to attach the lozenge unit to the handle is starch sodium octenyl succinate (E1450), confectioner's sugar (as sucrose and maize-starch) and purified water. Starch sodium octenyl succinate is a modified maize-based food starch.

The imprinting ink contains ethanol, purified water, de-waxed white shellac, propylene glycol, ammonium hydroxide and brilliant blue FCF CI42090.

The total glucose load per dosage unit from the dextrates is approximately 1.89 g per dose. [redacted]

Attachment 2b

Approved Product Information (clean) for;

ACTIQ fentanyl (as citrate) lozenge with integral applicator blister pack
(with changes highlighted)

[redacted]

PHARMACOLOGY

Pharmacodynamic properties

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. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, constipation, miosis, cough suppression and hyporeflexia.

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-naive 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.

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 depression is seen 15 to 30 minutes following the administration of ACTIQ, and may persist for several hours.

Pharmacokinetic Properties

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 in healthy adult male subjects after consumption of ACTIQ (200 micrograms to 1600 micrograms). T_{max} is around 20 to 40 minutes (range 20 - 480 minutes) after consumption of an ACTIQ unit.

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

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 (Vss) is 4 L/kg.

[redacted]

Metabolism

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/h/kg (range 0.3-0.7 L/h/kg). The terminal elimination half-life after ACTIQ administration is about 7 hours.

CLINICAL TRIALS

ACTIQ was investigated in clinical trials involving 257 opioid tolerant adult cancer patients experiencing breakthrough pain. Breakthrough cancer pain was defined as a transient flare of moderate to severe pain occurring in cancer patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 µg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

In two dose titration studies, 95 of 127 patients (75%), who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain, were titrated to a successful dose of ACTIQ to treat their breakthrough cancer pain within the dose range offered (200, 400, 600, 800, 1200 and 1600 micrograms). In these studies 11% of patients withdrew due to adverse events and 14% withdrew due to other reasons. A "successful" dose was defined as a dose where one unit of ACTIQ could be used consistently for at least two consecutive days to treat breakthrough cancer pain without unacceptable side effects.

The successful dose of ACTIQ for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and was best determined by dose titration.

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of ACTIQ for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 1.

Table 1 Successful Dose of ACTIQ Following Initial Titration

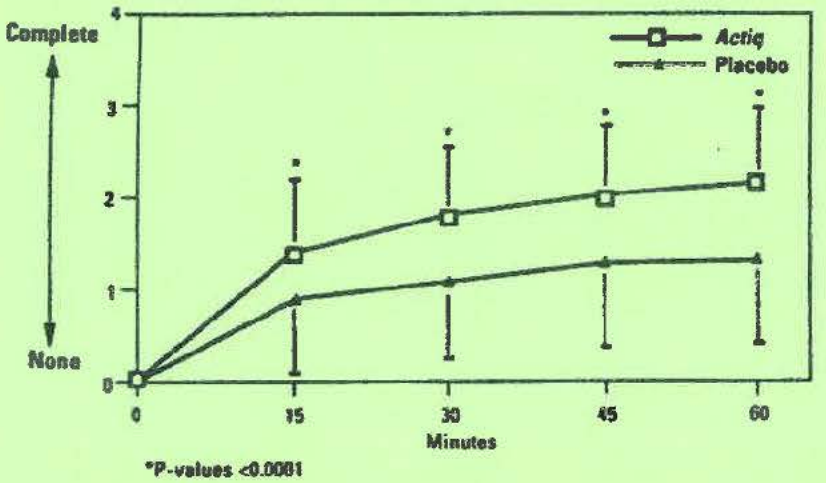
ACTIQ Dose	Total No. (%) (N=92)
200 µg	13 (14)
400 µg	19 (21)
600 µg	14 (15)
800 µg	18 (20)
1200 µg	13 (14)
1600 µg	15 (16)
Mean ± SD	789 ± 468 µg

On average, patients over 65 years of age titrated to a mean dose that was about 200 µg less than the mean dose to which younger adult patients were titrated.

[redacted]

ACTIQ produced statistically significantly more pain relief compared with placebo at 15, 30, 45 and 60 minutes following administration (see Figure 1).

Figure 1
Pain Relief (PR) Scores (Mean ± SD) During the Double-Blind Phase – All Patients with Evaluable Episodes on Both ACTIQ and Placebo (N=86)



In this same study patients also rated the performance of medication to treat their breakthrough cancer pain using a different scale ranging from "poor" to "excellent". On average, placebo was rated "fair" and ACTIQ was rated "good."

The safety of ACTIQ has been evaluated in these 257 opioid tolerant chronic cancer pain patients. The most common adverse events observed in ACTIQ clinical trials included somnolence, nausea, vomiting, and dizziness. Frequently, these adverse events ceased or decreased in intensity with continued use of ACTIQ, as the patient was titrated to the proper dose. There has been no attempt to correct for concomitant use of other opioids such as sustained-release morphine or transdermal fentanyl for persistent cancer pain; duration of ACTIQ therapy; or cancer-related symptoms. Thus, adverse events were included regardless of causality or severity.

In a separate multicentre, double-blind, double-dummy, randomised multiple-crossover study, the efficacy of ACTIQ (200 – 1600 µg) was compared against that of morphine sulfate immediate release (MSIR) (15 – 60 mg) for treatment of breakthrough pain in cancer patients taking stable around-the-clock (ATC) doses of opioids. Of the 134 patients who entered the study, 93 titrated to a dose of ACTIQ whereby a single unit of ACTIQ effectively treated an episode of breakthrough pain and entered the double-blind phase of the study. When stable and effective doses of each medication were compared in a double-blind fashion, ACTIQ produced significantly better efficacy measurements than MSIR at each time point evaluated in the double-blind phase for pain intensity, pain intensity difference, summed pain intensity difference, pain relief, and total pain relief scores at 15, 30, 45, and 60 minutes post study drug consumption. The most frequently observed adverse events associated with ACTIQ in this study, somnolence, nausea, constipation and dizziness, were consistent with those common to cancer patients receiving opioid therapy.

No trials have evaluated ACTIQ for the treatment of non-cancer related breakthrough pain.

[redacted]

INDICATIONS

ACTIQ is indicated for the management of breakthrough cancer pain in patients with malignancies who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain.

CONTRAINDICATIONS

ACTIQ is contraindicated in:

Hypersensitivity to fentanyl or any of the excipients (see **DESCRIPTION**).

Patients without maintenance opioid therapy as there is an increased risk of respiratory depression

Treatment of acute pain other than breakthrough pain (e.g. postoperative pain, headache, migraine)

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.

Non-opioid tolerant patients (see **PRECAUTIONS**).

PRECAUTIONS

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 taking ACTIQ.

Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 µg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl.

Opioid naive Patients
Due to the risk of respiratory depression, which may occur at any dose of ACTIQ in patients not chronically exposed to opioids, ACTIQ is contraindicated in opioid naïve patients.

Special Risk Patients
Respiratory:
As with all opioids, there is a risk of respiratory depression associated with the use of ACTIQ and patients should be monitored closely for symptoms when initiating therapy or when their dose is changed.

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.

Head injuries and increased intracranial pressure:
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,

[redacted]

or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

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

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

Hypersensitivity
Hypersensitivity (including anaphylaxis and anaphylactic shock) has been reported in association with the use of fentanyl.

Serotonin syndrome
Caution is advised when fentanyl is coadministered with drugs that affect the serotoninergic neurotransmitter systems.
The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). 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 fentanyl should be discontinued.

Diabetics:
Diabetic patients should be advised that the medicine 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.

Hepatic and Renal Impairment
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.

Carcinogenicity, Mutagenicity, Impairment of Fertility
The carcinogenic potential of fentanyl has not been investigated. Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test and mouse lymphoma thymidine kinase assay) and chromosomal damage (mouse micronucleus test).

In humans, the prolonged use of opiate analgesics may result in impairment of fertility, infertility or sexual dysfunction in both sexes and menstrual disturbances in women. The impairment of fertility has been observed in female rats given fentanyl 0.16 mg/kg/day SC (no effect dose not established) or 0.4 mg/kg/day IV (no effect dose 0.1 mg/kg/day, associated with plasma fentanyl concentrations similar to or lower than those expected in humans using ACTIQ).

[redacted]

Use in 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 pregnancy (Category C)
Fentanyl crosses the placenta in humans and has been found in foetal blood at concentrations about 40% of those found in maternal blood. The safe use of fentanyl in pregnant women has not been established with respect to possible adverse effects on foetal development. Opiate analgesics used during labour may cause respiratory depression in the newborn infant and should be used only after weighing the needs of the mother against the risk to the foetus.

Administration of fentanyl at doses ≥0.03 mg/kg/day IV or SC to rats was associated with a prolonged delivery time and increased post-natal mortality of offspring. There was no evidence of teratogenic activity or of adverse effects on the development of surviving offspring. Plasma levels of fentanyl at the no effect dose in the rat studies were similar to those expected in humans during treatment with ACTIQ. A study in rabbits at IV doses up to 0.4 mg/kg/day showed no evidence of teratogenic activity.

Use in labour and delivery
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).

Use in Lactation
Fentanyl passes into breast milk, therefore women should not breastfeed while taking ACTIQ because of the possibility of sedation and/or respiratory depression in their infants. Breastfeeding should not be restarted until at least 6 days after the last administration of fentanyl.

Use in Children and adolescents
ACTIQ is not recommended for use in children and adolescents below 18 years since the appropriate posology and safety of ACTIQ have not been established in this population. The opioid maintenance dose, which constitutes adequate opioid tolerance for the use of ACTIQ, has not been investigated in children, or has the adequate dosage been identified.

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 or dizziness while taking ACTIQ.

INTERACTIONS WITH OTHER MEDICINES

Fentanyl is metabolised by cytochrome P450 3A4 isoenzyme in the liver and intestinal mucosa. Potent inhibitors of cytochrome P450 3A4 such as macrolide antibiotics, e.g. erythromycin, ketoconazole 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 cytochrome

[redacted]

P450 3A4. Hence caution is advised if fentanyl is given concomitantly with cytochrome P450 3A4 inhibitors.

Use with potent cytochrome P450 3A4 inducers may decrease the effect of fentanyl.

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.

Serotonergic Drugs
Coadministration of fentanyl with a serotonergic agent, such as a selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition.

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).

ADVERSE EFFECTS

The adverse events seen with ACTIQ are typical opioid side effects. Frequently, these opioid side effects will cease or decrease in intensity with continued use of ACTIQ, as the patient is titrated to the proper dose. Opioid side effects should be expected and managed accordingly.

The most serious adverse events associated with all opioids are respiratory depression, (potentially leading to apnoea or respiratory arrest), circulatory depression, hypotension, and shock. All patients should be monitored for symptoms of respiratory depression, which may manifest as somnolence.

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 adverse events considered to be at least possibly-related to treatment, from clinical trials involving 448 patients taking ACTIQ 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

[redacted]

Common headache, myoclonus, taste perversion
Uncommon: hyperaesthesia

Eye disorders
Uncommon: abnormal vision

Vascular disorders
Common: vasodilatation

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea

Gastrointestinal disorders
Very common: nausea, constipation
Common: vomiting, dry mouth, dyspepsia, mouth ulcers/stomatitis, tongue disorder, abdominal pain
Uncommon: abdomen enlarged, flatulence

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

Post Marketing Experience

The following adverse reactions have been reported with ACTIQ during post marketing experience:

Anorexia, hypersensitivity reactions (including rash erythema, lip and face swelling and urticaria)sedation, loss of consciousness, circulatory depression, respiratory arrest, respiratory depression, hypotension, vertigo, coma, shock, convulsion, paraesthesia (including hyperaesthesia/circumoral paraesthesia), abnormal gait/incoordination, ileus, dental caries, tooth loss, gingival recession, gingivitis, gingival bleeding, anaphylactic reaction, tongue oedema, , weight decrease, slurred speech, pharyngeal oedema, application site reactions including gum bleeding, irritation, pain and ulcer, malaise.

DOSAGE AND ADMINISTRATION

ACTIQ is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent (around the clock) cancer pain.

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. Physicians should keep in mind the potential for abuse of fentanyl. All patients with opioids require careful monitoring for signs of abuse and addiction.

[redacted]

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 BTP when switching to ACTIQ.

The number of ACTIQ strengths available to the patient at any time should be minimized 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.

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 not be 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.

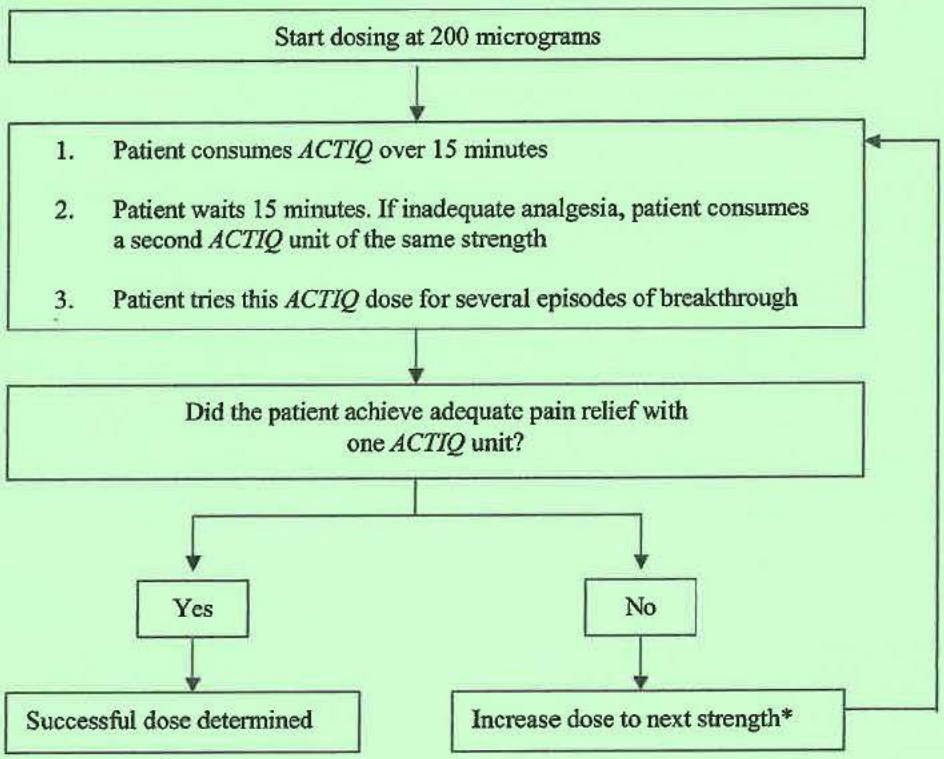
It is recommended that patients should wait at least 4 hours before treating another BTP episode with ACTIQ during titration.

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 1600 micrograms, a second dose is only likely to be required by a minority of patients.

If treatment of several 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.

[redacted]

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.

Breakthrough pain episodes may vary in intensity. In these cases, a second dose of the same strength may be used 30 minutes after starting the first dose. If a second dose of ACTIQ is required for several consecutive BTP episodes, the usual maintenance dose is to be readjusted (see below).

It is recommended that patients should wait at least 4 hours before treating another BTP episode with ACTIQ during maintenance.

c) **Dose re-adjustment**

The maintenance dose of ACTIQ should be increased when a patient requires more than one dose per BTP episode 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, 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.

[redacted]

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

d) 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.

Instructions for use, handling and disposal

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 medications may add to this risk.

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 reach and sight of children and to discard open and unopened units appropriately.

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

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

OVERDOSAGE

Acute Toxicity and Symptoms

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 effects being altered mental status, loss of consciousness, coma, cardiorespiratory arrest, respiratory depression, respiratory distress and respiratory failure, which have resulted in death.

Management and Treatment

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 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 Product Information of the individual opioid antagonist for details about such use.

[redacted]

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.

PRESENTATION AND STORAGE CONDITIONS

ACTIQ is available as a lozenge with integral applicator, in six unit strengths of 200 micrograms, 400 micrograms, 600 micrograms, 800 micrograms, 1200 micrograms and 1600 micrograms of fentanyl base. The radio-opaque handle is marked with the name and dosage strength.

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, 9, 15 or 30 individual units. Not all pack sizes are marketed in Australia.

Storage conditions
Store below 30^0C.

NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty Ltd
(a member of the Aspen Australia group of companies)
34-36 Chandos Street
St Leonards NSW 2065
Australia

POISON SCHEDULE OF THE MEDICINE

S8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

15 November 2002

DATE OF MOST RECENT AMENDMENT

31 July 2014

ACTIQ is a registered trademark of Anesta LLC., a division of Cephalon, Inc., USA, used under licence by Orphan Australia Pty Ltd.

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