# AUSTRALIAN PRODUCT INFORMATION – ACTIQ® (FENTANYL CITRATE) LOZENGE

## WARNINGS

### Limitations of use

Because of the risks associated with the use of opioids, ACTIQ should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see Section 4.4 Special Warnings and Precautions for Use).

### Hazardous and harmful use

ACTIQ poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see Section 4.4. Special Warnings and Precautions for Use).

### Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of ACTIQ. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see Section 4.4 Special Warnings and Precautions for Use).

### Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking ACTIQ.

# 1 NAME OF THE MEDICINE

Fentanyl citrate

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIQ (fentanyl citrate) is a synthetic opioid analgesic related to pethidine and with similar properties to morphine. Fentanyl citrate is a white, crystalline powder.

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 lozenges are 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.

Excipients with known effect: dextrates approximately 1.89 g per dose of Actiq. For the full list of excipients, see Section 6.1 List of excipients.

# 3 PHARMACEUTICAL FORM

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.

# 4 CLINICAL PARTICULARS

## 4.1 THERAPEUTIC 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.

## 4.2 DOSE AND METHOD OF 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.

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 (see Section 6.4 Special precautions for storage). 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.

### 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.

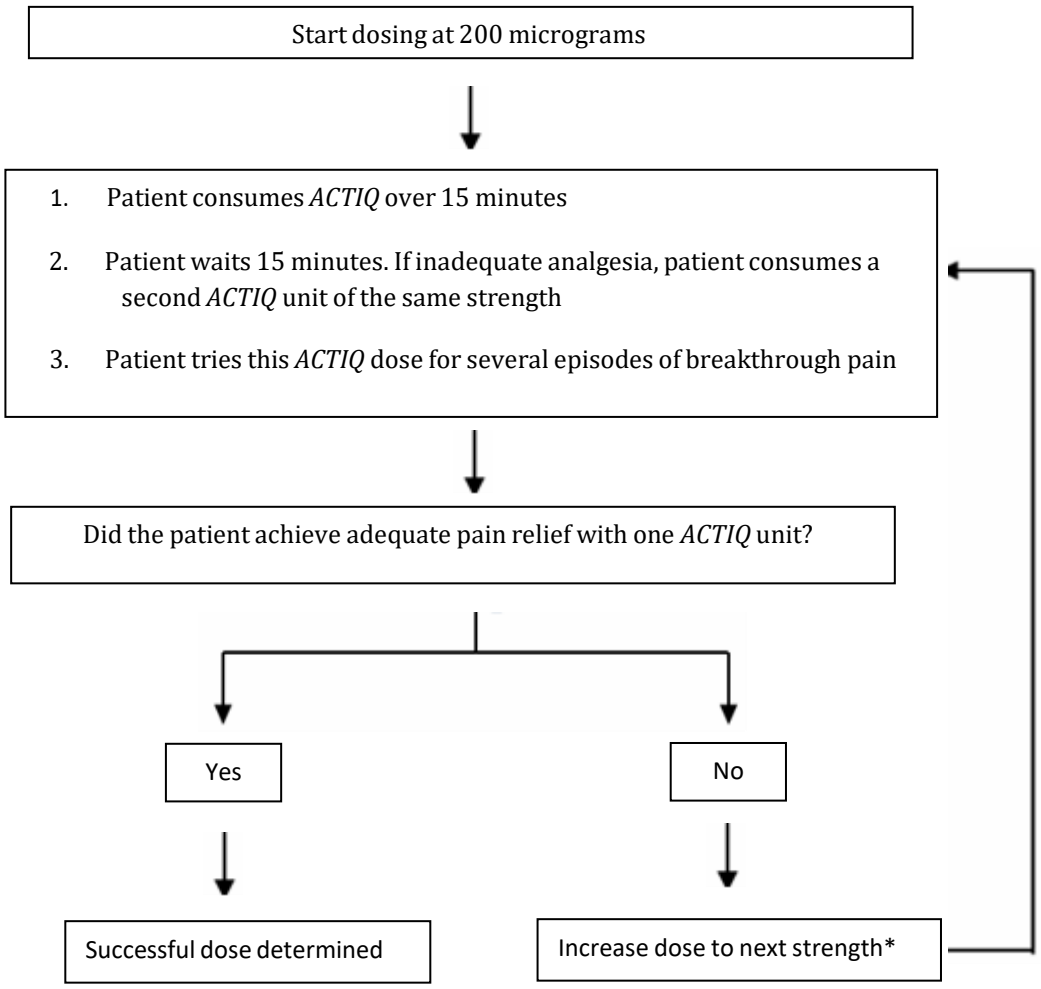
The initial dose of ACTIQ used should be 200 micrograms, titrating upwards as necessary through the range of available dosage strengths (200, 400, 600, 800, 1200 and 1600 micrograms). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable side 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.

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.

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.

**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.

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.

**Instructions for use and handling:**
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.

## 4.3 CONTRAINDICATIONS

ACTIQ is contraindicated in:

- Hypersensitivity to fentanyl or any of the excipients (see Section 6.1 List of excipients).
- Patients without maintenance opioid therapy as there is an increased risk of respiratory depression.
- Treatment of non-breakthrough cancer pain.
- Treatment of acute and chronic non-cancer 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 disease, severe obstructive lung conditions, acute respiratory disease and respiratory depression.
- Opioid naive patients (see Section 4.4 Special warnings and precautions for use).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Product must not be used in opioid non-tolerant patients. Life-threatening respiratory depression could occur at any dose in patients not taking chronic opiates (see Section 4.4 – Respiratory Depression). Deaths have occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing (see Section 4.4 – Opioid naive Patients).

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.

### Hazardous and harmful use

ACTIQ contains the opioid fentanyl citrate and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed ACTIQ at recommended doses. However, iatrogenic addiction following therapeutic use of opioids is known to occur.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed ACTIQ.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share ACTIQ with anyone else.

### Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of ACTIQ but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see Section 4.3 Contraindications). Titrate fentanyl citrate cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with impaired hepatic, renal or respiratory function (e.g. chronic obstructive pulmonary disease; asthma).For further information, refer to Section 4.4, Special Warnings and Precautions for Use - 'Use in the elderly' and 'Use in hepatic and renal impairment'. Opioids should be used with caution and with close monitoring in these patients (see Section 4.2 Dose and method of administration).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2 Dose and method of administration)

together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

### Respiratory disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (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 opioid dosage using best practices for opioid taper.

### Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol and gabapentinoids (gabapentin or pregabalin)

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol and gabapentinoids (gabapentin or pregabalin), may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of ACTIQ with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe ACTIQ concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking ACTIQ.

### Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid. Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

If discontinuation of all opioid therapy is required, Actiq may be immediately ceased while the other maintenance opioid should be withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2 Dose and Method of Administration).

### Accidental ingestion/exposure

Accidental ingestion or exposure of ACTIQ, especially by children, can result in a fatal overdose of fentanyl citrate. Patients and their caregivers should be given information on safe storage and disposal of unused ACTIQ (see Section 6.4 Special precautions for storage and Section 6.6 Special precautions for disposal).

### Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

### Ceasing opioids

For patients no longer requiring their prolonged opioid therapy for the baseline cancer pain control, the ACTIQ dose should be taken into consideration, before the gradual downward titration of other opioids, to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, ACTIQ therapy can be discontinued immediately (see Section 4.2 Dose and Method of Administration; Discontinuation of therapy). The treatment by chronic opioids for the baseline cancer pain should be kept as prescribed. If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor.

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see Section 4.2 Dose and Method of Administration). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

### 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. Full or partially consumed fentanyl citrate lozenges contain medicine in an amount that can be fatal.

### Delirium

The risk of delirium is relevant for medicinal products containing fentanyl including products for transmucosal route of administration and fixed dose combination products.

### 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,

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

**Cardiac disease/bradycardia:**
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), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), 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.

**MAO inhibitors:**
Fentanyl citrate is contraindicated for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

**Dental Decay:**
Because fentanyl citrate lozenges contain approximately 1.89 grams of sugar per unit, 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 should be made aware of this sugar content (see section 4.4. – Diabetics).

**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.

**Use in hepatic and renal impairment:**
ACTIQ should be used with caution in patients with renal or hepatic impairment because of the hepatic metabolism and renal excretion of fentanyl. 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.

**Endocrine Disorders:**
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.

**Adrenal insufficiency:**
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.

**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.

**Paediatric use**
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.

**Neonatal Withdrawal Syndrome**
See Section 4.6 Use in pregnancy.

**Effects on laboratory tests**
No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Fentanyl is metabolised mainly by the cytochrome P450 3A4 isoenzyme (CYP3A4) in the liver and intestinal mucosa, therefore potential interactions may occur when ACTIQ is given concurrently with agents affecting CYP3A4 activity.

The concomitant use of ACTIQ with strong CYP3A4 inhibitors such as macrolide antibiotics, e.g. 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. This may also result in increased fentanyl plasma concentrations, potentially causing serious

adverse drug reactions including fatal respiratory depression, hypotension and profound sedation (see Section 4.4, Special warnings and precautions for use – Respiratory Depression). Consider dosing adjustments if warranted. Similar effects could be seen after concurrent ingestion of moderate CYP3A4 inhibitors e.g. amprenivir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil, which is known to inhibit cytochrome P450 3A4. Patients receiving ACTIQ concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done with caution.

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

The concomitant use of other CNS depressants, including gabapentinoids (gabapentin and pregabalin) and other opioids, cannabis, tricyclic antidepressants, antipsychotics, centrally-active anti-emetics, sedatives (e.g. benzodiazepines) or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects. Refer to Section 4.4, Special Warnings and Precautions for Use–Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol and gabapentinoids (gabapentin and pregabalin). Dosage adjustment maybe required.

**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 (see Section 4.3 Contraindications).

**Partial Opioid Agonists or Opioid Agonist-Antagonists:**
Partial opioid agonists (e.g. buprenorphine) and opioid agonist-antagonists (e.g., nalbuphine, pentazocine, butorphanol) have high affinity to opioid receptors with relatively low intrinsic activity. The concomitant use of partial opioid agonists or opioid agonist-antagonists may partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients.

Withdrawal symptoms may therefore 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 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**
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).

**Use in pregnancy – Pregnancy Category C**
Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

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.

Prolonged use of fentanyl lozenges during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognised and treated, and requires management according to protocols developed by neonatology experts. 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.

Fentanyl crosses the placenta in humans and has been found in foetal blood at concentrations about 40% of those found in maternal blood. For this reason, it is advised not to use fentanyl during delivery as it 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.

## 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 or dizziness while taking ACTIQ.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE 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

Common headache, myoclonus, taste perversion Uncommon: hyperaesthesia

Other adverse reactions from clinical studies (frequency unknown): vertigo, coma, abnormal gait/ coordination, convulsion, mental status changes

**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, dysphagia

Other adverse reactions from clinical studies (frequency unknown): dental caries, tooth loss, gingival recession, ileus

**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

Other adverse reactions from clinical studies (frequency unknown): Application site reactions including gum bleeding, irritation, pain and ulcer

**Injury, poisoning and procedural complications**
Common: accidental injury

**Post Marketing Experience**
The following adverse reactions have been reported with ACTIQ during post marketing experience:

**Immune system disorders:**
Hypersensitivity reactions (including rash erythema, lip and face swelling and urticaria), tongue oedema anaphylactic reaction

**Endocrine disorders:**
Adrenal insufficiency, androgen deficiency

**Metabolism and nutrition disorders:**
Anorexia

**Nervous system disorders:**
Loss of consciousness, slurred speech, paraesthesia (including hyperaesthesia/circumoral paraesthesia), sedation

**Cardiac disorders:**
Circulatory depression, hypotension

**Vascular disorders:**
Shock

**Respiratory, thoracic and mediastinal disorders:**
Respiratory arrest, pharyngeal oedema, respiratory depression

**Gastrointestinal disorders:**
Gingival bleeding, gingivitis

**General disorders and administration site conditions:**
Drug withdrawal syndrome including reports of neonatal withdrawal syndrome (see also Section 4.6 Fertility, pregnancy and lactation), drug dependence (see also Section 4.4 Identified Precautions, "Tolerance, dependence and withdrawal") and drug abuse (see also Section "Special warnings, precautions for use")

**Investigations:**
Weight decrease

**Reporting suspected adverse effects**
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting- problems.

## 4.9 OVERDOSE

**Clinical presentation:**
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.

Leukoencephalopathy has also been observed with fentanyl overdose.

**Immediate 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.

**Treatment of overdosage (accidental ingestion) in the opioid non-tolerant person**
For treatment of overdosage (accidental ingestion) in the opioid naive person, obtain intravenous access, and employ naloxone or other opioid antagonists 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.

**Treatment of overdose in opioid tolerant 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**
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.

### 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 |

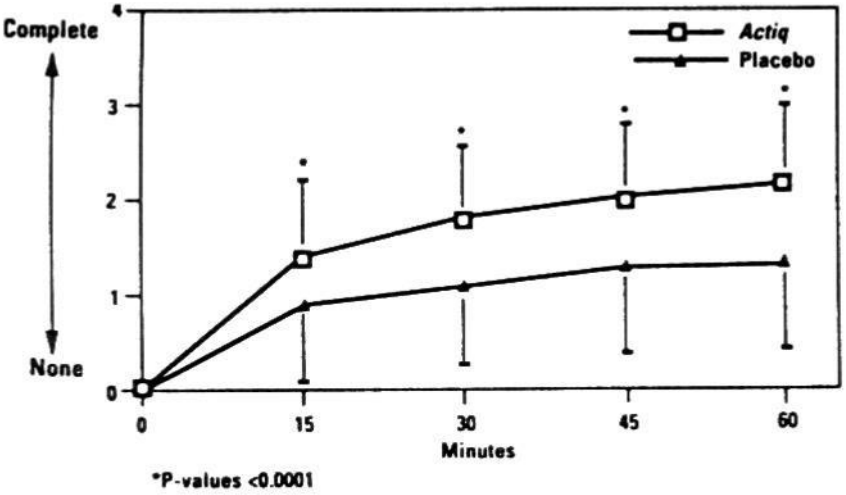
On average, patients over 65 years of age titrated to a mean dose that was about 200 µg less than the mean dose to which younger adult patients were titrated.

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.

## 5.2 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. Cmax ranges from 0.39 to 2.51 ng/mL in healthy adult male subjects after consumption of ACTIQ (200 micrograms to 1600 micrograms). Tmax 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.

### 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.

### Excretion

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.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

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).

### Carcinogenicity

Carcinogenicity studies (26-week dermal bioassay in Tg.AC transgenic mice; two-year subcutaneous study in rats) did not induce any findings indicative of oncogenic potential. Evaluation of brain slides from the

carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown. At the highest doses tested

in these studies (50 µg/day in mice, 50 µg/kg/day in male rats and 100 µg/kg/day in female rats), systemic exposure (plasma Cmax in mice and AUC in rats) was about 3-fold (mice and female rats) and about 2-fold (male rats) that observed following a single dose of 800 µg fentanyl in humans.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

The compressed powder dosage unit contains dextrates (93% glucose monohydrate, as D-glucose, and 7% maltodextrin), citric acid, 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 de-waxed white shellac and brilliant blue FCF (CI42090).

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

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30$^{o}$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, 9, 15 or 30 individual units. Not all pack sizes are marketed in Australia.

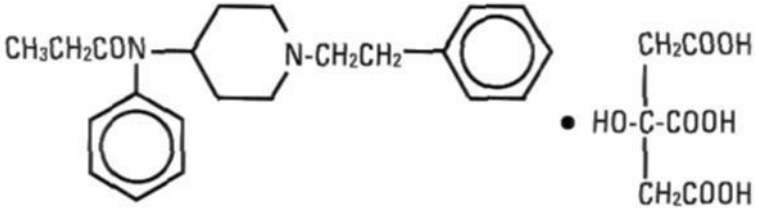
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**




**Molecular weight**
528.6

**Molecular Formula**
$C_{22}H_{28}N_2O,C_6H_8O_7$

**Chemical Name**
N-(1-Phenethyl-4-piperidyl) propionanilide dihydrogen citrate

**CAS number**
990-73-8

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8

# 8 SPONSOR

Teva Pharma Australia Pty Ltd

Level 1, 37 Epping Rd

Macquarie Park NSW 2113

Telephone: 1800 28 8382

Website: www.tevapharma.com.au

ACTIQ is a registered trademark of Teva Pharmaceutical Industries Limited.

# 9 DATE OF FIRST APPROVAL

15 November 2002

# 10 DATE OF REVISION

12 September 2024

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| **4.8** | Addition of dysphagia, in line with CCSI |
| **4.9** | Addition of Leukoencephalopathy has also been observed with fentanyl overdose, in line with CCSI |