AUSTRALIAN PRODUCT INFORMATION – FENTORA (FENTANYL CITRATE) ORALLY DISINTEGRATING TABLETS

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, FENTORA 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

FENTORA 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 FENTORA. 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 FENTORA.

1 NAME OF THE MEDICINE

Fentanyl citrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see Section 6.1, LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

FENTORA orally disintegrating tablets are available in five unit strengths equivalent to 100, 200, 400, 600 and 800 micrograms of fentanyl base.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FENTORA is indicated for the treatment of breakthrough pain (BTP) in adults with cancer who are already receiving maintenance opioid therapy for chronic cancer pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated by and remain under the guidance of a physician experienced in the management of opioid therapy in cancer patients. Physicians should keep in mind the potential of abuse of fentanyl. All patients treated with opiods require careful monitoring for signs of abuse and addiction.

Patients should be instructed not to use two different formulations of fentanyl concurrently for the treatment of breakthrough pain, and to dispose of any fentanyl product prescribed for BTP when switching to FENTORA. The number of tablet strengths available to the patients at any time should be minimised to prevent confusion and potential overdose.

Dose titration

FENTORA should be individually titrated to an “effective” dose that provides adequate analgesia and minimises undesirable effects. In clinical studies, the effective dose of FENTORA for BTP was not predictable from the daily maintenance dose of opioid. Patients should be carefully monitored until an effective dose is reached.

Titration in patients not switching from other fentanyl containing products

The initial dose of FENTORA should be 100 micrograms, titrating upwards as necessary through the range of available tablets strengths (100, 200, 400, 600, 800 micrograms).

Titration in patients switching from other fentanyl containing products

Due to different absorption profiles, switching must not be done at a 1:1 ratio. If switching from another oral fentanyl citrate product, independent dose titration with FENTORA is required as bioavailability between products differs significantly, especially when a different route of administration is used. However, in these patients, a starting dose higher than 100 micrograms may be considered.

Method of administration:

FENTORA tablets once exposed to moisture utilises an effervescent reaction to deliver the active substance. Therefore patients should be instructed not to open the blister until ready to place the tablet in the buccal cavity.

Opening the blister package

Patients should be instructed NOT to attempt to push the tablet through the blister because this could damage the orally disintegrating tablet. The correct method of releasing the tablet from the blister is:

By separating one blister unit from the blister card by tearing it apart at the perforations. The blister unit should then be flexed along the line printed on the backing foil where indicated. The backing foil should be peeled back to expose the tablet.

Patients should be instructed not to attempt to crush or split the tablet.

The tablet should not be stored once removed from the blister package as the tablet integrity cannot be guaranteed and a risk of accidental exposure to a tablet can occur.

Method of titration

During titration, if adequate analgesia is not obtained within 30 minutes after the start of administration of a single tablet, a second FENTORA tablet of the same strength may be used.

If treatment of a BTP episode requires more than one tablet, an increase in dose to the next higher available strength should be considered to treat the next BTP episode.

During titration, multiple tablets may be used: up to four 100 micrograms or up to four 200 micrograms tablets may be used to treat a single episode of BTP during dose titration according to the following schedule:

- If the initial 100 micrograms tablet is not efficacious, the patient can be instructed to treat the next episode of BTP with two 100 micrograms tablets. It is recommended that one tablet should be placed in each side of the mouth. If this dose is considered to be the effective dose, treatment of successive episodes of BTP may be continued with a single 200 micrograms tablet of FENTORA.

- If a single 200 micrograms tablet of FENTORA (or two 100 micrograms tablets) is not considered to be efficacious the patient can be instructed to use two 200 micrograms tablets (or four 100 micrograms tablets) to treat the next episode of BTP. It is recommended that

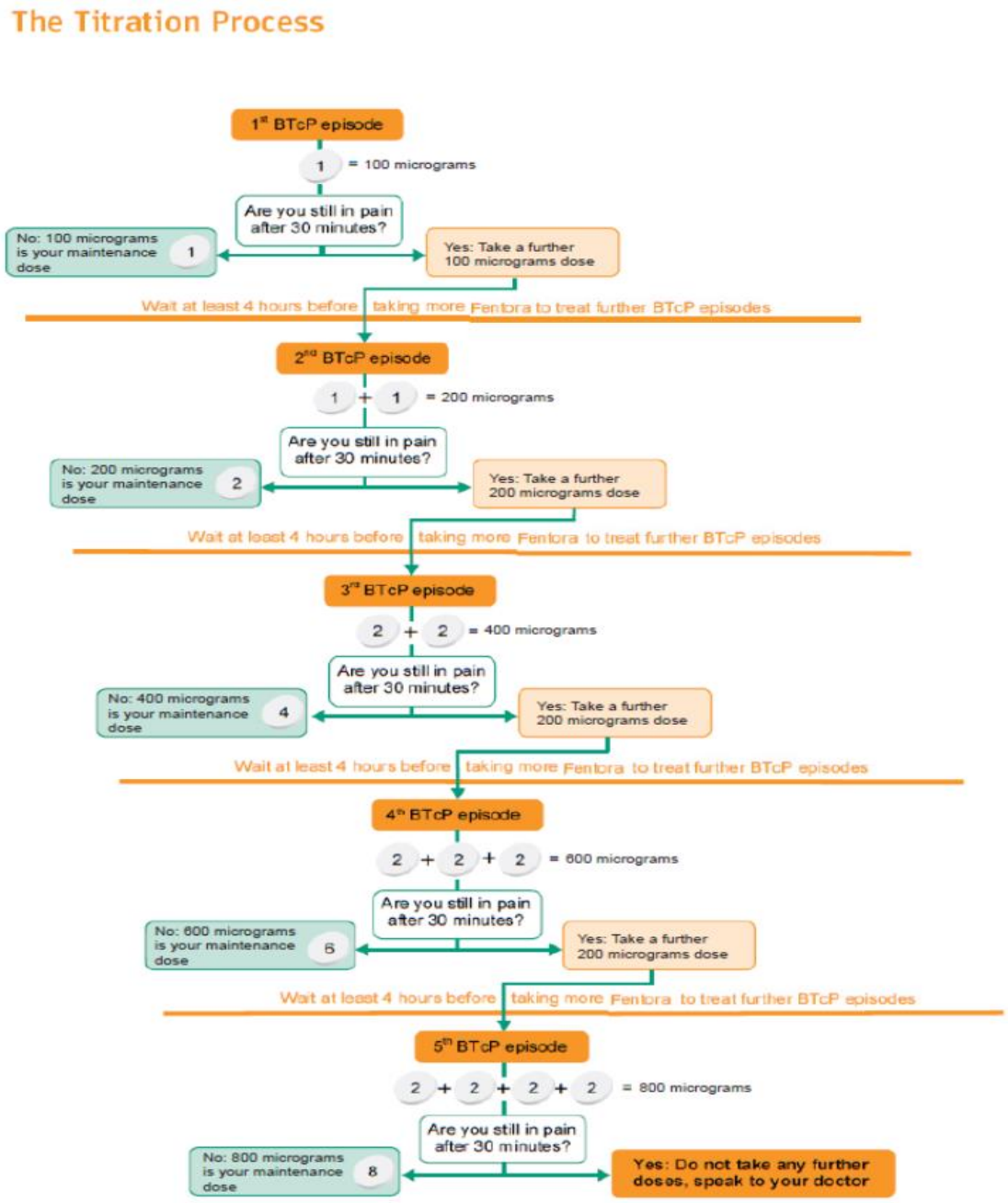
two tablets should be placed in each side of the mouth. If this dose is considered to be the effective dose, treatment of successive episodes of BTP may be continued with a single 400 micrograms tablet of FENTORA.

- For titration to 600 micrograms and 800 micrograms, tablets of 200 micrograms should be used.

Doses above 800 micrograms were not evaluated in clinical studies.

No more than two tablets should be used to treat any individual BTP episode, except when titrating using up to four tablets as described above.

Patients should wait at least 4 hours before treating another BTP episode with FENTORA during titration. The frequency may be increased under clinical supervision.



Maintenance therapy

Once an effective dose has been established during titration, patients should continue to take this dose as a single tablet of that given strength. Breakthrough pain episodes may vary in intensity and the required FENTORA dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of FENTORA was required for several consecutive times, the usual maintenance dose is to be readjusted (see below).

Patients should wait at least 4 hours before treating another BTP episode with FENTORA during maintenance therapy. The frequency may be increased under clinical supervision.

Dose readjustment

The maintenance dose of FENTORA should be increased when a patient requires more than one tablet per BTP episode for several consecutive BTP episodes. For dose-readjustment the same principles apply as outlined for dose titration (see above).

Dose readjustment of the background opioid therapy may be required if patients consistently present with more than four BTP episodes per 24 hours. If the dose of background opioid therapy is increased, the dose of FENTORA to treat BTP may need to be reviewed.

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

Patients with xerostomia:

Patients experiencing xerostomia are advised to drink water to moisten the buccal cavity prior to administration of FENTORA. If this recommendation does not result in an appropriate effervescence, then a switch of therapy may be advised.

Tablet administration:

Patients should remove the tablet from the blister unit and immediately place the entire FENTORA tablet in the buccal cavity (near a molar between the cheek and gum). Alternatively, the tablet could be placed sublingually (under the tongue at the deepest part) (see Section 5.2 PHARMACOKINETICS PROPERTIES).

The FENTORA tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

FENTORA should be placed and retained within the buccal cavity or sublingual cavity for a period sufficient to allow disintegration of the tablet which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the FENTORA tablet remain, they may be swallowed with a glass of water.

The length of time that the tablet takes to fully disintegrate following oromucosal administration does not appear to affect early systemic exposure to fentanyl.

Patients should not consume any food and drink when a tablet is in the buccal cavity.

In case of buccal mucosa irritation, a change in tablet placement within the buccal cavity should be recommended.

Discontinuation of therapy:

FENTORA therapy may usually be immediately discontinued if no longer required for BTP 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 FENTORA dose in consideration of a gradual downward opioid titration to avoid the possibility of abrupt withdrawal effects.

4.3 CONTRAINDICATIONS

FENTORA is contraindicated in:

- Hypersensitivity to the active substance or to any of the excipients (see Section 6.1, LIST OF EXCIPIENTS).
- Patients without maintenance opioid therapy (see Section 5.1, PHARMACODYNAMICS PROPERTIES, clinical trials) as there is an increased risk of respiratory depression.
- Severe respiratory disease, severe obstructive lung conditions, acute respiratory disease and respiratory depression.
- Treatment of acute and chronic pain (e.g. postoperative pain, headache, migraine) other than breakthrough cancer pain.
- Simultaneous use of monoamine-oxidase (MAO) inhibitors, or within 2 weeks after the cessation of the use of MAO inhibitors.
- 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

FENTORA is contraindicated for use in opioid non-tolerant patients. Life-threatening respiratory depression could occur at any dose in patients not taking chronic opiates (see Section 4.3 – CONTRAINDICATIONS and Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Respiratory Depression). Deaths have occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing.

In order to minimise the risks of opioid-related undesirable effects and to identify the effective dose, it is imperative that patients be monitored closely by health professionals during the titration process.

It is important that the long acting opioid treatment used to treat the patient's persistent pain has been stabilised before FENTORA therapy begins and that the patient continues to be treated with the long acting opioid treatment whilst taking FENTORA.

When switching from another oral fentanyl citrate product, independent dose titration is required as bioavailability between products differ significantly.

Hazardous and harmful use
FENTORA contains the opioid fentanyl citrate and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed FENTORA 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 FENTORA.

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 FENTORA 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 FENTORA 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, severe obstructive lung conditions, acute respiratory disease and respiratory depression (see Section 4.3 CONTRAINDICATIONS). Titrate fentanyl citrate buccal tablets cautiously in patients with chronic obstructive pulmonary disease or pre-existing 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. In general, careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response. When prescribing or dispensing Fentora, do not convert patients on a microgram-per-microgram (1:1) basis from other fentanyl products to Fentora due to different absorption profiles (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Respiratory 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 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 FENTORA 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 FENTORA 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 FENTORA.

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). 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 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Partial Opioid Agonists or Opioid Agonist-Antagonists). 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, Fentora 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).

MAO inhibitors
Fentanyl buccal tablets are not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

***Accidental ingestion*/exposure**
Accidental ingestion or exposure of FENTORA, 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 FENTORA (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 FENTORA 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, FENTORA therapy can be discontinued immediately. 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.

Chronic obstructive pulmonary disease*:*

Particular caution should be used when titrating FENTORA in patients with non-severe chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression, as even normally therapeutic doses of FENTORA may further decrease respiratory drive to the point of respiratory failure.

Increased intracranial pressure, impaired consciousness:

FENTORA 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. In clinical trials with FENTORA, no clear evidence for bradycardia was observed. However, FENTORA should be used with caution in patients with pre-existing bradyarrhythmias.

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

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.

Application site:

Application site reactions, including gum bleeding, irritation, pain and ulcer have been reported in post-marketing use. Therefore caution is advised for patients with mucositis and local tolerability issues.

Controlled sodium diet:

This medicinal product contains 10 mg sodium per 100 micrograms tablet, and 20 mg sodium per 400, 600 and 800 micrograms tablet. To be taken into consideration by patients on a controlled sodium diet.

Anaphylaxis and hypersensitivity:

Anaphylaxis and hypersensitivity have been reported in association with the use of oral transmucosal fentanyl products.

Endocrine disorders and adrenal insufficiency:

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 buccal tablets, 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.

Neonatal Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in pregnancy).

Use in hepatic and renal impairment

FENTORA should be administered with caution to patients with hepatic or renal impairment because of the hepatic metabolism and renal excretion of fentanyl. When administered intravenously the clearance of fentanyl has been shown to be altered in hepatic and renal impairment due to alterations in metabolic clearance and plasma proteins. After administration of FENTORA, impaired hepatic 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 impairment.

Use in the elderly

In clinical studies patients older than 65 years tended to titrate to a lower effective dose than younger patients. It is recommended that increased caution should be exercised in titrating the dose of FENTORA in elderly patients.

Paediatric use

FENTORA is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Fentanyl is metabolised mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4), therefore potential interactions may occur when FENTORA is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of FENTORA with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, and nelfinavir) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and

verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug reactions. These can include respiratory depression, hypotension and profound sedation (see Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Respiratory Depression). Consider dosage adjustments if warranted. Patients receiving FENTORA concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done with caution.

Coadministration with agents that induce 3A4 activity may reduce the efficacy of FENTORA.

The concomitant use of other central nervous system 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, 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).

FENTORA is not recommended 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 (See Section 4.3, CONTRAINDICATIONS).

Partial Opioid Agonists or Opioid Agonist-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 dependent patients.

Serotoninergic Drugs:

Coadministration of fentanyl with a serotoninergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

When male rats treated with fentanyl for 28 days prior to and during mating were mated with untreated females, adverse effects on sperm parameters, which reduced fertility, were observed at a high subcutaneous dose of 300 µg/kg/day that also resulted in mortalities. No effects on fertility were observed following administration of the same dose to females mated with untreated males. Estimated fentanyl exposure (plasma AUC) at this dose was about 10-fold that observed following a single dose of 800 µg fentanyl in humans and about 2-fold that observed after four daily doses of 800 µg fentanyl. Corresponding exposure ratios at the no observed effect level for fertility (100 µg/kg/day) were 3 and 0.6.

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.

Fentanyl crosses the placenta in humans and has been found in fetal blood at concentrations about 40% of those found in maternal blood. Hence, do not use fentanyl buccal tablets during labour and delivery.

There are no adequate data from the use of fentanyl in pregnant women. In studies in which fentanyl was administered to rats and rabbits at respective subcutaneous doses of up to 100 and 250 µg/kg/day during the period of organogenesis, no increased incidence of fetal malformations or variations was observed, but fetal weights were reduced in rats at the maternotoxic dose of 100 µg/kg/day. Respective fentanyl exposures (plasma AUC) at these doses in rats and rabbits were about 3- and 5-fold that observed following a single dose of 800 µg fentanyl in humans, and less than or equal to that observed in humans after four daily doses of 800 µg fentanyl.

In a study in which rats received subcutaneous fentanyl from early gestation to weaning, reduced pup survival, growth and development were observed at clearly maternotoxic doses (100 and 400 µg/kg/day). Fentanyl exposure (plasma AUC) at the no-effect dose for pup developmental toxicity (50 µg/kg/day) was similar to that observed following a single dose of 800 µg fentanyl in humans and about 0.2-fold that observed after four daily doses of 800 µg fentanyl.

Prolonged use of fentanyl buccal tablets 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 (see also Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

FENTORA should not be used in pregnancy unless clearly necessary.

Use in lactation

Following long-term treatment, fentanyl may cause withdrawal in the new-born infant.

Fentanyl passes into breast milk and may cause sedation and respiratory depression in the breast-fed child. Fentanyl should not be used by breastfeeding women and 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

As a class of medicines, opioid analgesics 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, or visual disturbance while taking FENTORA and not to drive or operate machinery until they know how they react. The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Because the clinical studies of FENTORA were designed to evaluate safety and efficacy in treating BTP, 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 FENTORA alone.

The table below summarises the adverse events occurring during the titration and post-titration periods in at least 5% of patients with cancer and breakthrough pain from three Phase 3 studies in patients with cancer and BTP:

Table 1: Summary of Adverse events occurring during titration and post-titration

MedDRA system organ class Preferred term, n (%)	**Percentage of patients (%)**		
	Titration period (N=358)	**Posttitration period (N=239)**	**Overall (N=358)**
Patients with at least 1 adverse event	206 (58)	217 (91)	305 (85)
Blood and lymphatic system disorders			
Anaemia	6 (2)	31 (13)	40 (11)
Neutropenia	3 (<1)	15 (6)	18 (5)
Gastrointestinal disorders			
Nausea	59 (16)	71 (30)	110 (31)
Vomiting	19 (5)	51 (21)	63 (18)
Constipation	15 (4)	34 (14)	48 (13)
Diarrhoea	8 (2)	22 (9)	29 (8)
Abdominal pain	5 (1)	25 (10)	27 (8)
Stomatitis	8 (2)	13 (5)	20 (6)
Dyspepsia	1 (<1)	12 (5)	13 (4)
General disorders and administration site conditions			
Fatigue	20 (6)	40 (17)	58 (16)
Oedema peripheral	5 (1)	32 (13)	38 (11)
Asthenia	6 (2)	27 (11)	34 (9)
Pyrexia	4 (1)	19 (8)	23 (6)
Infections and infestations			
Pneumonia	3 (<1)	21 (9)	24 (7)
Urinary tract infection	4 (1)	15 (6)	18 (5)
Investigations			
Weight decreased	4 (1)	18 (8)	22 (6)
Metabolism and nutrition disorders			
Dehydration	10 (3)	24 (10)	33 (9)
Anorexia	3 (<1)	23 (10)	25 (7)
Hypokalaemia	5 (1)	13 (5)	18 (5)

Musculoskeletal and connective tissue disorders			
Arthralgia	3 (<1)	17 (7)	22 (6)
Back pain	5 (1)	16 (7)	20 (6)
Pain in extremity	2 (<1)	11 (5)	14 (4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
Cancer pain	3 (<1)	12 (5)	15 (4)
Nervous system disorders			
Dizziness	64 (18)	28 (12)	83 (23)
Headache	28 (8)	31 (13)	52 (15)
Somnolence	21 (6)	22 (9)	41 (11)
Psychiatric disorders			
Depression	1 (<1)	24 (10)	25 (7)
Anxiety	4 (1)	15 (6)	20 (6)
Confusional state	4 (1)	16 (7)	18 (5)
Insomnia	2 (<1)	14 (6)	16 (4)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	6 (2)	18 (8)	23 (6)
Cough	3 (<1)	16 (7)	19 (5)

The following adverse reactions have been reported with FENTORA during clinical studies and post marketing experience. Adverse reactions are listed below 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, rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data); within each frequency group, undesirable effects are presented in order of decreasing seriousness:

Table 2: Frequency of Adverse Events reported during clinical studies and post marketing experience:

	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Investigations		Weight decreased	Platelet count decreased Heart rate increased Haematocrit decreased Haemoglobin decreased		
Cardiac disorders		Tachycardia	Bradycardia		
Blood and lymphatic system disorders		Anaemia Neutropenia	Thrombocyto-penia		

	Very common	Common	Uncommon	Rare	Not known
Nervous system disorders	Dizziness Headache	Dysgeusia Somnolence Lethargy Tremor Sedation Hypoaesthesia Migraine	Depressed level of consciousness Disturbance in attention Balance disorder Dysarthria	Cognitive disorder Motor dysfunction	Loss of consciousness Convulsion
Eye disorders			Visual disturbance Ocular hyperaemia Blurred vision Visual acuity reduced	Abnormal sensation in eye Photopsia	
Ear and labyrinth disorders			Vertigo Tinnitus Ear discomfort		
Respiratory, thoracic and mediastinal disorders		Dyspnoea Pharyngolaryn-geal pain	Respiratory depression Sleep apnoea syndrome		Respiratory arrest
Gastro-intestinal disorders	Nausea Vomiting	Constipation Stomatitis Dry mouth Diarrhoea Abdominal pain Gastro-oesophageal reflux disease Stomach discomfort Dyspepsia Toothache	Ileus Mouth ulceration Oral hypoaesthesia Oral discomfort Oral mucosal discolouration Oral soft tissue disorder Glossodynia Tongue blistering Gingival pain Tongue ulceration Tongue disorder Oesophagitis Chapped lips Tooth disorder	Oral mucosal blistering Dry lip	
Renal and urinary disorders			Urinary retention		

	Very common	Common	Uncommon	Rare	Not known
Skin and subcutaneous tissue disorders		Pruritus Hyperhidrosis Rash	Cold sweat Facial swelling Generalised pruritus Alopecia	Onychorrhexis	
Musculoskeletal and connective tissue disorders		Myalgia Back pain	Muscle twitching Muscular weakness		
Endocrine disorders				Hypogonadism	Adrenal insufficiency, androgen deficiency
Metabolism and nutrition disorders		Anorexia			
Infections and infestations		Oral candidiasis	Pharyngitis	Oral pustule	
Injury, poisoning and procedural complications		Fall			
Vascular disorders		Hypotension Hypertension	Flushing Hot flush		
General disorders and administration site conditions	Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles	Peripheral oedema Fatigue Asthenia Drug withdrawal syndrome Chills	Malaise Sluggishness Chest discomfort Feeling abnormal Feeling jittery Thirst Feeling cold Feeling hot		Drug tolerance, neonatal withdrawal syndrome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.6, FERTILITY, PREGNANCY AND LACTATION, and drug abuse (see also Section 4.4, SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Hepatobiliary disorders			Biliary dilatation		

	Very common	Common	Uncommon	Rare	Not known
Psychiatric disorders		Depression Anxiety Confusional state Insomnia	Euphoric mood Nervousness Hallucination Visual hallucination Mental status changes Drug dependence (addiction) Disorientation		Hallucinations Delirium
Immune system disorders				Hypersensitivity (including rash, erythema, lip and face swelling, and urticaria)	

Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as fentanyl. Neonatal withdrawal syndrome may also develop (see Section 4.6, FERTILITY, PREGNANCY AND LACTATION)

Opioid withdrawal symptoms such as nausea, vomiting, diarrhoea, anxiety and shivering have been observed in studies with FENTORA.

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 manifestations of fentanyl buccal tablets 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, hypotension, respiratory depression, respiratory distress, and respiratory failure, which have resulted in death.

Immediate management

Immediate management of opioid overdose includes removal of the FENTORA orally disintegrating tablet, 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 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 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 FENTORA, 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 is an opioid analgesic, interacting predominantly with the opioid μ-receptor. Its primary therapeutic actions are analgesia and sedation. Secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria.

The analgesic effects of fentanyl are related to its plasma level. In general, the effective concentration and the concentration at which toxicity occurs increases with increasing tolerance to opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of FENTORA should be individually titrated to achieve the desired effect (see Section 4.2, DOSE AND METHOD OF ADMINISTRATION).

All opioid μ-receptor agonists, including fentanyl, produce dose dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy as these patients will develop tolerance to respiratory depressant effects.

Clinical trials

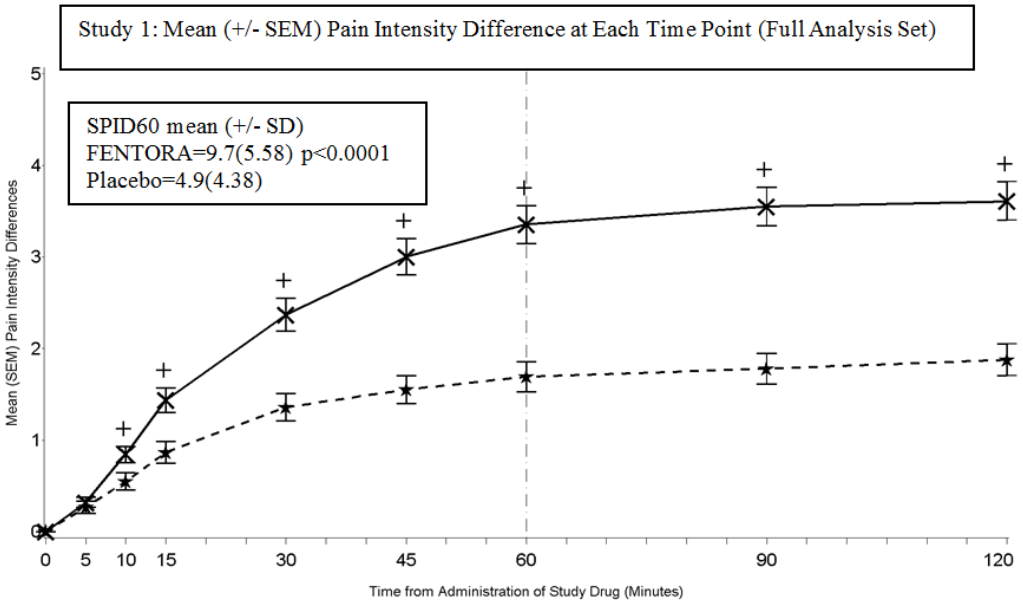
The safety and efficacy of FENTORA have been evaluated in patients taking the drug at the onset of the breakthrough pain episode. BTP is a transitory exacerbation of pain that occurs on a background of otherwise controlled persistent pain. Pre-emptive use of FENTORA for predictable pain episodes was not investigated in the clinical trials.

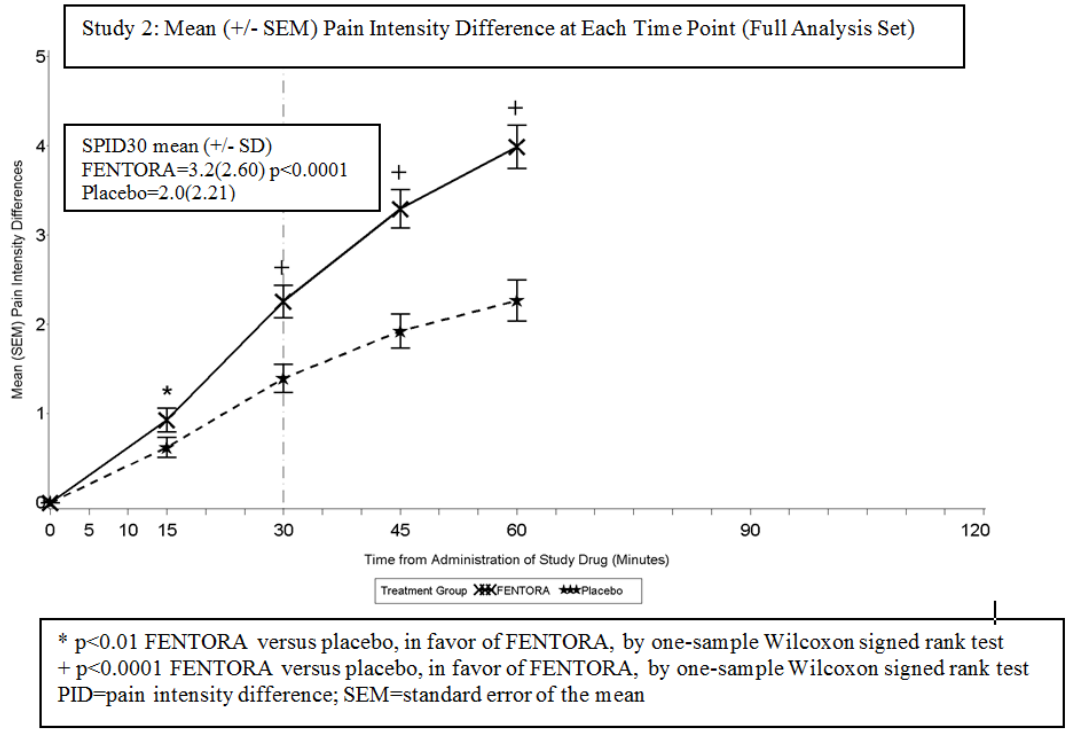
Two double-blind, randomized, placebo-controlled crossover studies have been conducted involving a total of 248 patients with BTP and cancer who experienced on average 1 to 4 episodes of BTP per day while taking maintenance opioid therapy. Patients receiving maintenance opioid therapy are those who are 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.

During an initial open-label phase, patients were titrated to an effective dose of FENTORA. Patients who identified an effective dose entered the double-blind phase of the study. The primary efficacy variable was the patient's assessment of pain intensity. Patients assessed pain intensity on an 11-point scale. For each BTP episode, pain intensity was assessed prior to and at several time points after treatment.

Sixty-seven percent of the patients were able to be titrated to an effective dose.

In the pivotal clinical study (study 1), the primary endpoint was the average sum of differences in pain intensity scores from dosing to 60 minutes, inclusive (SPID60), which was statistically significant compared to placebo ($p<0.0001$).





In the second pivotal study (study 2), the primary endpoint was SPID30, which was also statistically significant compared to placebo (p<0.0001).

Statistically significant improvement in pain intensity difference was seen with FENTORA versus placebo as early as 10 minutes in Study 1 and as early as 15 minutes (earliest time point measured) in Study 2. These differences continued to be significant at each subsequent time point in each individual study.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

FENTORA employs a delivery technology which utilises an effervescent reaction which enhances the rate and extent of fentanyl absorbed through the buccal mucosa. Transient pH changes accompanying the effervescent reaction may optimise dissolution (at a lower pH) and membrane permeation (at a higher pH).

Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not affect early systemic exposure to fentanyl. In addition, a comparative study evaluating the absorption of one 400 microgram FENTORA tablet administered either buccally (i.e., between the cheek and the gum) or sublingually met the criteria of bioequivalence.

Following oromucosal administration of FENTORA, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of FENTORA is largely the result of an initial rapid absorption from the buccal mucosa, with peak plasma concentrations following venous sampling

generally attained within an hour after oromucosal administration. Approximately 50% of the total dose administered is rapidly absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and slowly absorbed from the gastrointestinal tract where 30% of it becomes systemically available by bypassing hepatic and intestinal first-pass elimination.

The main pharmacokinetic parameters are shown in the following table.

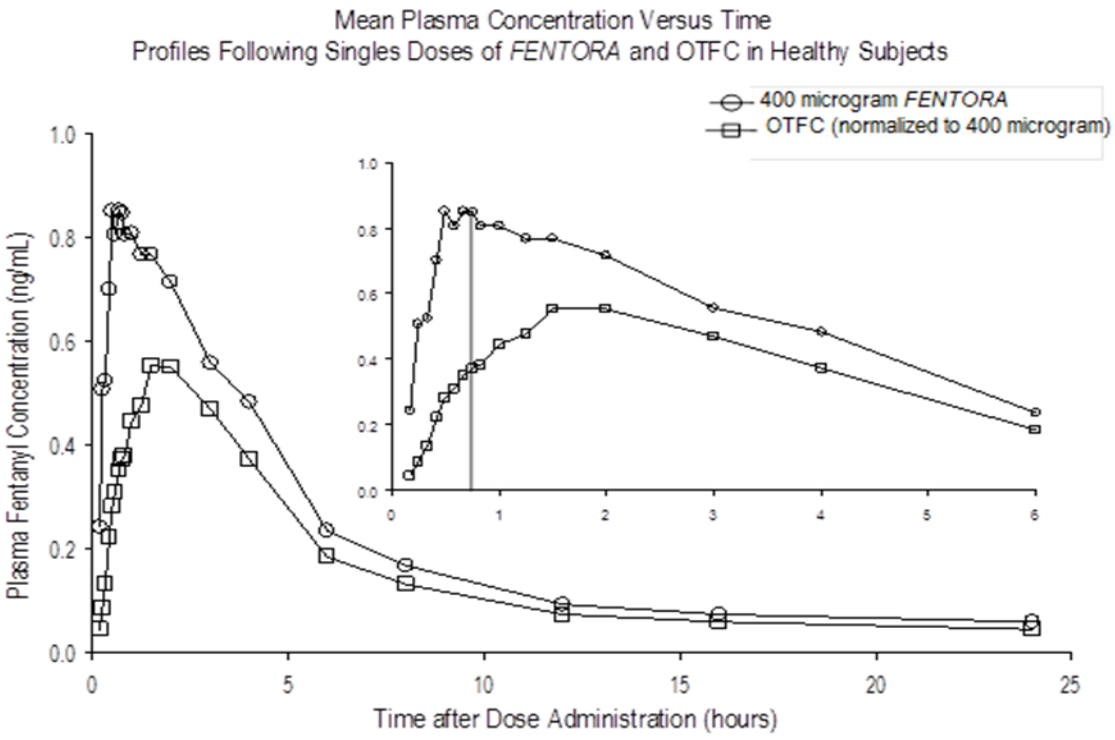
Pharmacokinetic Parameters in Adult Subjects Receiving FENTORA*

Table 3: Summary of Pharmacokinetic Properties

Pharmacokinetic parameter (mean)	FENTORA 400 micrograms
Absolute bioavailability	65% (±20%)
Fraction absorbed transmucosally	48% (±31.8%)
T_{max} (minute) **	46.8 (20-240)
C_{max} (ng/ml)	1.02 (± 0.42)
$AUC_{0\text{-}tmax}$ (ng.hr/ml)	0.40 (± 0.18)
$AUC_{0\text{-}inf}$ (ng.hr/ml)	6.48 (± 2.98)

* Based on venous blood samples (plasma). Fentanyl citrate concentrations obtained in serum were higher than in plasma: Serum AUC and Cmax were approximately 20% and 30% higher than plasma AUC and Cmax, respectively. The reason of this difference is unknown.
** Data for Tmax presented as median (range).

In pharmacokinetic studies that compared the absolute and relative bioavailability of FENTORA and oral transmucosal fentanyl citrate (OTFC), the rate and extent of fentanyl absorption in FENTORA demonstrated exposure that was between 30% to 50% greater than that for oral transmucosal fentanyl citrate. If switching from another oral fentanyl citrate product, independent dose titration with FENTORA is required as bioavailability between products differs significantly. However, in these patients, a starting dose higher than 100 micrograms may be considered.



OTFC data were dose adjusted (800 microgram to 400 microgram)

Differences in exposure with FENTORA were observed in a clinical study with patients with grade 1 mucositis. Cmax and AUC0-8 were 1% and 25% higher in patients with mucositis compared to those without mucositis, respectively. The differences observed were not statistically or clinically significant.

Dose proportionality from 100 micrograms to 1000 micrograms of FENTORA has been demonstrated.

Distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution. After buccal administration of FENTORA, fentanyl undergoes initial rapid distribution that represents an equilibration of fentanyl between plasma and the highly perfused tissues (brain, heart and lungs). Subsequently, fentanyl is redistributed between the deep tissue compartment (muscle and fat) and the plasma.

The plasma protein binding of fentanyl is 80% to 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.

Metabolism

The metabolic pathways following buccal administration of FENTORA have not been characterised in clinical studies. 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

Following the intravenous administration of fentanyl, less than 7% of the administered 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.

Following the administration of FENTORA, the terminal elimination phase of fentanyl is the result of the redistribution between plasma and a deep tissue compartment. This phase of elimination is slow, resulting in a median terminal elimination half-life t1/2 of approximately 22 hours following buccal administration of the effervescent formulation and approximately 18 hours following intravenous administration. The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test, mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA synthesis in rat hepatocytes, mammalian cell transformation assay). The genotoxic potential of fentanyl is considered to be low.

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 excipients include mannitol, sodium starch glycollate type A, sodium hydrogen carbonate, sodium carbonate, citric acid and magnesium stearate.

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 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

FENTORA orally disintegrating tablets are available in five unit strengths equivalent to 100, 200, 400, 600 and 800 micrograms of fentanyl base. The orally disintegrating tablets are flat-faced, round, beveled-edge tablet, embossed one side with a “C” and on the other side with “1” for FENTORA 100 micrograms, with “2” for FENTORA 200 micrograms, with “4” for FENTORA 400 micrograms, with “6” for FENTORA 600 micrograms, or with “8” for FENTORA 800 micrograms.

FENTORA is supplied in aluminium laminated blister of PVC/aluminium foil/Polyamide/PVC with paper/polyester/aluminium foil lidding.

Blister packs are supplied in cartons of 4 or 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

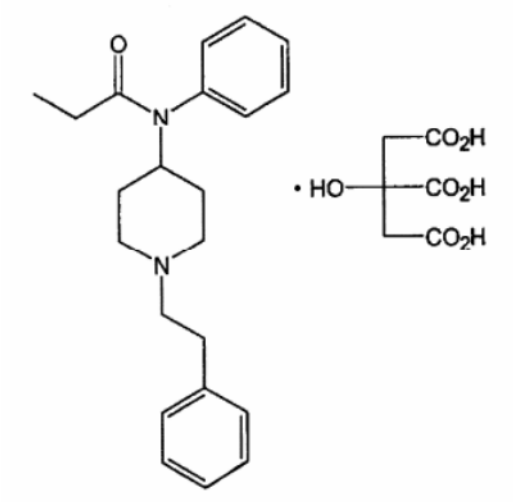
Patients and their carers must be instructed that FENTORA contains an active substance in an amount that can be fatal, especially to a child. Therefore they must keep all tablets out of the reach and sight of children.

Patients and carers must be advised to dispose of any unopened tablets remaining from a prescription as soon as they are no longer needed.

Medicines should not be disposed of via wastewater or household waste.In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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 288 382
Website: www.tevapharma.com.au

9 DATE OF FIRST APPROVAL

6 March 2015

10 DATE OF REVISION

05 June 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of precaution of concomitant use with gabapentinoids, in line with CCSI.
4.5	Addition of interaction with gabapentinoids, in line with CCSI.