PRODUCT MONOGRAPH

[N]TEVA-FENTANYL

Fentanyl Transdermal System

Patch, 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h and 100 mcg/h

Opioid Analgesic

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Transdermal	Patch Five strengths with 2.063 mg, 4.125 mg, 8.25 mg, 12.375 mg and 16.5 mg fentanyl per patch, delivering 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h fentanyl respectively for 72 hours	Backing film: backing foil Self adhesive drug containing the matrix: Polybutyltitanate, and Duro-Tak® Peelable release liner: Polyethyleneterepthalate (PET or PETP) foil

INDICATIONS AND CLINICAL USE

Adults:
TEVA-FENTANYL (fentanyl transdermal system) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment and:

- that is opioid-responsive;
- and for which alternative options are inadequate

Only for use in patients who are already receiving opioid therapy at a total daily dose of at least 60 mg/day Morphine Equivalents.

TEVA-FENTANYL is not indicated as an as-needed (prn) analgesic.

The initial dose of TEVA-FENTANYL should be obtained or calculated from the conversion tables (see **DOSAGE AND ADMINISTRATION**), and must **not** be higher than that dose which is equivalent to the total dose of opioids the patient is receiving at the time of the switch to the patch.

Because serious or life-threatening hypoventilation could occur, TEVA-FENTANYL should not

be used in:

- non-opioid-tolerant patients
- the management of post-operative pain

Pediatrics (< 18 years of age):
The safety and efficacy of fentanyl transdermal system has not been studied in the pediatric population. Therefore, the use of TEVA-FENTANYL in patients under 18 years of age is not recommended. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal system.

Geriatrics (> 65 years of age):
In elderly, cachectic, or debilitated patients, fentanyl transdermal system may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION**). Therefore, it may be appropriate, according to clinical judgment, to initiate these patients on a lower TEVA-FENTANYL dose than that which the conversion tables recommend, including the use of the 12 mcg/h dose by itself or in combination with another dose, provided the patient is not opioid-naive (see **CONTRAINDICATIONS**). The 12 mcg/h strength may also be used for dose titration up or down, as using small increments for dose adjustment is recommended to enhance tolerability of opioid therapy (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Because serious or life-threatening hypoventilation could occur, TEVA-FENTANYL is contraindicated in:

1) patients with acute or perioperative pain, especially use in out-patient or day surgeries (**see WARNINGS AND PRECAUTIONS, Perioperative Considerations**);
2) patients with mild, intermittent or short duration pain that can otherwise be managed;
3) opioid-naive patients, at any dose,
4) situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment;
5) patients who have acute or severe bronchial asthma;
6) patients who are hypersensitive to the active substance (fentanyl) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph;
7) patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type);
8) patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis);
9) patients with acute alcoholism, delirium tremens, and convulsive disorders;
10) patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury;

11) patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy);
12) women who are breast-feeding, pregnant, or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS** and **WARNINGS AND PRECAUTION**S).

Because serious or life-threatening hypoventilation could occur, the maximum initiation dose of TEVA-FENTANYL should not be higher than that equivalent to the total dose of opioids the patient is receiving at the time of the switch (see conversion tables in **DOSAGE AND ADMINISTRATION**).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, TEVA-FENTANYL should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse
TEVA-FENTANYL poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing TEVA-FENTANYL, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). TEVA-FENTANYL should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE
Serious, life-threatening, or fatal respiratory depression may occur with use of TEVA-FENTANYL. Infants exposed in-utero or through breast milk are at risk of lifethreatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of TEVA-FENTANYL or following a dose increase. Placing the TEVA-FENTANYL patch in the mouth, chewing it, swallowing it or using it in any way other than indicated may cause choking or overdose that could result in death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids: addiction, tolerance and fatal overdose.

Accidental Exposure
Serious medical consequences, including death, may occur if people, especially children, are accidentally exposed to TEVA-FENTANYL. Examples of accidental exposure include

transfer of TEVA-FENTANYL while hugging, sharing a bed, or moving a patient (see DOSAGE AND ADMINISTRATION subsection Disposal of TEVA-FENTANYL Patch, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of TEVA-FENTANYL during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interactions with Alcohol
The co-ingestion of alcohol with TEVA-FENTANYL should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of TEVA-FENTANYL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General
Use in non-opioid-tolerant patients, or use of an initiating dose which is higher than the opioid equivalent to which the patient is tolerant at the time of the switch, may lead to fatal respiratory depression.

The following contraindications reduce the potential risk of serious or life-threatening hypoventilation: TEVA-FENTANYL should not be used in the management of acute or post-operative pain since there is no opportunity for dose titration during short-term use and serious or life-threatening hypoventilation could result. Similarly, TEVA-FENTANYL should not be administered to patients who do not have some degree of tolerance to opioid-induced side effects. TEVA-FENTANYL should ONLY be prescribed to patients who require continuous opioids for pain management, and who are tolerant to at least the morphine equivalent of the lowest initiating TEVA-FENTANYL dose.

The initial dose of TEVA-FENTANYL should be obtained from the conversion tables in DOSAGE AND ADMINISTRATION, and must not be higher than that dose which is equivalent to the total dose of opioids the patient is receiving at the time of the switch to the patch. It may be appropriate, according to clinical judgment, to initiate some patients on a lower TEVA-FENTANYL dose than that which the conversion tables recommend, which

may include use of the 12 mcg/h dose. Opioid-naive patients should not be given TEVA-FENTANYL at any dose, inclusive of 12 mcg/h (see CONTRAINDICATION). In general, the 12 mcg/h dose, which allows for smaller dose increases than does the 25 mcg/h patch, is to be used for titration/adjustments of dosage (see DOSAGE AND ADMINISTRATION).

TEVA-FENTANYL should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain and in the detection and management of respiratory depression including the use of opioid antagonists.

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER TEVA-FENTANYL REMOVAL, OR MORE, AS CLINICAL SYMPTOMS DICTATE, BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 20 to 27 HOURS LATER.

Due to the formation of a subcutaneous depot of fentanyl, not only does continued exposure occur after system removal but, in the case of removal prior to attainment of peak fentanyl exposure, fentanyl plasma levels may, in fact, continue to increase after removal of TEVA-FENTANYL patches.

TEVA-FENTANYL patches are intended for transdermal use on intact skin only; use on compromised skin can lead to increased exposure to fentanyl.

Risk of Unintentional Increase in Drug Exposure

Patients with Fever: Serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C (104°F) due to temperature-dependent increases in fentanyl release from the system and increased skin permeability. Patients who develop fever should be monitored for opioid side effects and have their TEVA-FENTANYL dose adjusted if necessary.

External Heat Sources: There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the fentanyl transdermal system increased mean fentanyl AUC values by 2.2-fold and mean C_{max} values by 61%. All patients should be advised to avoid exposing the TEVA-FENTANYL application site to direct external heat sources, such as heating pads, electric blankets, heated waterbeds, heat lamps, hot water bottles, saunas and hot whirlpool spa baths, intensive sunbathing, etc.

Cardiovascular

Cardiac disease:

Intravenous fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.

Hypotension: fentanyl may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or the concurrent administration of drugs such as phenothazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or certain anesthetics (see also **DRUG INTERACTIONS**). These patients should be monitored for signs of hypotension after initiating or titrating the dose of TEVA-FENTANYL. The use of TEVA-FENTANYL in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure. Fentanyl may also produce orthostatic hypotension in ambulatory patients.

Concomitant Use of CYP3A4 Inhibitors and Inducers

The concomitant use of TEVA-FENTANYL with potent cytochrome P450 3A4 inhibitors (including, but not limited to, ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In this situation, close monitoring and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patient is closely monitored, for an extended period of time, for signs of respiratory depression, with dosage adjustments made as warranted (see **DRUG INTERACTIONS**).

Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in TEVA-FENTANYL -treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions including respiratory depression. When using TEVA-FENTANYL with CYP3A4 inducers, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur (see **DRUG INTERACTIONS**).

Addiction, Abuse and Misuse

TEVA-FENTANYL is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, TEVA-FENTANYL should be prescribed and handled with caution. Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as TEVA-FENTANYL, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Since TEVA-FENTANYL may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs (see **Dependence/Tolerance**).

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of TEVA-FENTANYL and there is a potential for development of psychological dependence. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g. major depression).

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **DOSAGE AND ADMINISTRATION, Decreased Dosing or Discontinuation of TEVA-FENTANYL**).

Do not abruptly discontinue TEVA-FENTANYL in a patient physically dependent on opioids. There have been reports that rapid tapering of fentanyl in a patient physically dependent on opioids may lead to serious withdrawal symptoms and uncontrolled pain (see **DOSAGE AND ADMINISTRATION, Decreased Dosing or Discontinuation of TEVA-FENTANYL**).

Drug or Alcohol Dependence
Use of TEVA-FENTANYL in combination with CNS depressants, including alcohol, can result in increased risk to the patient (see **DRUG INTERACTIONS**).

TEVA-FENTANYL should be used with caution in individuals who have a history of drug or alcohol abuse, especially those outside a medically controlled environment. While the management of severe pain in patients with a history of addiction requires special consideration, the use of opioids is not necessarily contraindicated in these patients. There may also be an increased risk of diversion in this population; this risk may be decreased by attention to patterns of prescription requests, and by prescribing opioids only as part of an ongoing relationship between a patient and a healthcare provider. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to TEVA-FENTANYL unless used under extreme caution and awareness.

"Drug seeking" behaviour includes emergency calls or visits near the end of office hours; refusal to undergo appropriate examination, testing or referral; repeated "loss" of prescriptions; tampering with prescriptions; "doctor shopping" to obtain additional prescriptions; and reluctance to provide prior medical records or contact information for other treating physician(s).

Neurologic

Use in Patients with Convulsive or Seizure Disorders: The fentanyl in TEVA-FENTANYL may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Therefore, TEVA-FENTANYL should not be used in these patients (see **CONTRAINDICATIONS**).

Serotonin syndrome: Caution is advised when TEVA-FENTANYL is co-administered with drugs that affect the serotonergic neurotransmitter systems. The concomitant administration of TEVA-FENTANYL and serotonergic drugs (e.g. anti-depressants, anxiolytics, migraine medications) could cause serotonin syndrome, a rare but potentially life-threatening condition. This may occur within the recommended dose. If such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma and/or gastrointestinal symptoms such as nausea, vomiting, diarrhea) occur, the healthcare professional should determine whether treatment with TEVA-FENTANYL and/or the serotoninergic drug should be discontinued and supportive symptomatic treatment should be initiated. TEVA-FENTANYL should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Interactions with Central Nervous System (CNS) Depressants (Including benzodiazepines, alcohol and some illegal drugs): TEVA-FENTANYL should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants including alcohol and some illegal drugs. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, the lowest effective dosages and minimum duration for both drug should be prescribed. Patients should be carefully monitored for signs of respiratory depression and sedation (see **DRUG INTERACTIONS**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for

signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when TEVA-FENTANYL is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

TEVA-FENTANYL should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS** and **DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injuries and Increased Intracranial Pressure

TEVA-FENTANYL should not be used in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. TEVA-FENTANYL should be used with caution in patients with brain tumours.

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of TEVA-FENTANYL is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Perioperative Considerations

TEVA-FENTANYL is contraindicated for perioperative pain relief, especially in the elective surgical setting. In the case of planned chordotomy, or other pain-relieving operations, patients should not be treated with TEVA-FENTANYL within 72 hours before the operation and should not be used in the immediate post-operative period. Thereafter, if TEVA-FENTANYL is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief, if needed, and to reduce the risk of withdrawal in highly opioid-tolerant patients.

The administration of analgesics in the perioperative period should be managed by health care providers with adequate training and experience (e.g., an anesthesiologist) (see **CONTRAINDICATIONS)**

Hepatic/Biliary/Pancreatic
Because of the hepatic metabolism of fentanyl, TEVA-FENTANYL should be used with caution in patients with liver dysfunction.

TEVA-FENTANYL may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like TEVA-FENTANYL may cause increases in the serum amylase concentration.

If patients with hepatic impairment receive TEVA-FENTANYL, they should be observed carefully for signs of fentanyl toxicity and the dose of TEVA-FENTANYL reduced if necessary. (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Psychomotor Impairment
TEVA-FENTANYL may impair the mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients using TEVA-FENTANYL should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Renal
Because of the renal excretion of fentanyl, TEVA-FENTANYL should be used with caution in patients with kidney dysfunction.

If patients with renal impairment receive TEVA-FENTANYL, they should be observed carefully for signs of fentanyl toxicity and the dose should be reduced if necessary. The pharmacokinetic properties of fentanyl have not been studied in this population and, therefore, caution is warranted (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Treatment with fentanyl should only be considered in patients with kidney dysfunction if the benefits outweigh the risks.

Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.
While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of TEVA-FENTANYL, the risk is greatest during the initiation of therapy or following a dose increase. However, the risk of hypoventilation increases at serum fentanyl concentrations

greater than 2 ng/mL in non-opioid-tolerant patients, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to TEVA-FENTANYL (see **DRUG INTERACTIONS**). Patients should be closely monitored for respiratory depression when initiating therapy with TEVA-FENTANYL and following dose increases. As with other drug-level measurements, serum fentanyl concentrations may be useful clinically, although they do not reflect patients' sensitivity to fentanyl and should not be used by physicians as a sole indicator of effectiveness or toxicity.

The duration of the respiratory depressant effect of TEVA-FENTANYL may extend beyond the removal of the system (see also **OVERDOSAGE** concerning respiratory depression).

To reduce the risk of respiratory depression, proper dosing and titration of TEVA-FENTANYL is essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the TEVA-FENTANYL dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia) (see **ADVERSE REACTIONS**). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids. (see **DOSAGE AND ADMINISTRATION, Decreased Dosing or Discontinuation of TEVA-FENTANYL**).

Endocrine

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Gastrointestinal Tract

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with TEVA-FENTANYL should be stopped (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).**

Patients with Chronic Pulmonary Disease
Fentanyl should be used with caution in patients with chronic pulmonary disease, patients with decreased respiratory reserve and others with potentially compromised respiration. Normal analgesic doses of opioids may further decrease respiratory drive in these patients to the point of respiratory failure.

Information for Patients
Consumer Information is included in the package of TEVA-FENTANYL patches dispensed to the patient.

Patients receiving TEVA-FENTANYL patches should be given the following instructions by the physician:

1. Patients should be informed that accidental exposure or use by individuals (including children and pets) other than the patient for whom it was originally prescribed, may lead to severe, even fatal, consequences.
2. Patients should be advised that TEVA-FENTANYL patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone.
3. Patients should be advised that each TEVA-FENTANYL patch may be worn continuously for 72 hours, and that each patch should be applied to a different skin site after removal of the previous transdermal patch.
4. Patients should be advised that TEVA-FENTANYL patches should be applied to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. Additionally, patients should be advised of the following:
    - In young children or persons with cognitive impairment, the patch should be put on the upper back to lower the chances that the patch will be removed and placed in the mouth.
    - Hair at the application site should be clipped (not shaved) prior to patch application.
    - If the site of TEVA-FENTANYL application must be cleansed prior to application of the patch, do so with clear water.
    - Do not use soaps, oils, lotions, alcohol, or any other agents that may irritate the skin or alter its characteristics.
    - Allow the skin to dry completely prior to patch application.

5. Patients should be advised that TEVA-FENTANYL should be applied immediately upon removal from the sealed package and after removal of the protective liner.

Additionally the patient should be advised of the following:

- The TEVA-FENTANYL patch should not be used if the seal is broken, or if it is altered, cut, or damaged in any way prior to application. The transdermal patch should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.
- The patch should not be folded so that only part of the patch is exposed.

6. Patients should be advised that, while wearing the patch, they should avoid exposing the TEVA-FENTANYL application site to direct external heat sources, such as:
   - heating pads,
   - electric blankets,
   - heat lamps,
   - saunas,
   - hot tubs, and
   - heated waterbeds, etc.

7. Patients should be advised that there is a potential for temperature-dependent increase in fentanyl release from the patch that could result in an overdose of fentanyl; therefore, if patients develop a high fever while wearing the patch they should contact their physician.

8. Patients should be advised that if they experience problems with adhesion of the TEVA-FENTANYL patch, they may tape the edges of the patch with first aid tape. If problems with adhesion persist, patients may overlay the patch with a transparent adhesive film dressing.

9. Patients should be advised that if the patch falls off before 72 hours a new patch may be applied to a different skin site.

10. Patients should be advised to fold (so that the adhesive side adheres to itself) used TEVA-FENTANYL patches after removal from the skin and return to a pharmacy for proper disposal.

11. Patients should be instructed that, if the drug adhesive layer accidentally contacts the skin, the area should be washed clean with clear water and not soap, alcohol, or other chemicals, because these products may increase the ability of fentanyl to go through the skin.

12. Patients should be advised that the dose of TEVA-FENTANYL should NEVER be adjusted without the prescribing health care professional's instruction.

13. Patients should be advised that TEVA-FENTANYL may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).

14. Patients should be advised to refrain from any potentially dangerous activity when starting on TEVA-FENTANYL or when their dose is being adjusted, until it is established that they have not been adversely affected.

15. Patients should be advised that TEVA-FENTANYL should not be combined with alcohol or other CNS depressants (e.g. sleep medications, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

16. Patients should be advised to consult their physician or pharmacist if other medications are being or will be used with TEVA-FENTANYL.

17. Patients should be advised of the potential for severe constipation.

18. Patients should be advised that if they have been receiving treatment with TEVA-FENTANYL and cessation of therapy is indicated, it may be appropriate to taper the TEVA-FENTANYL dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

19. Patients should be advised that TEVA-FENTANYL contains fentanyl, a drug with high potential for abuse.

20. Patients, family members and caregivers should be advised to protect TEVA-FENTANYL from theft or misuse in the work or home environment.

21. Patients should be advised that TEVA-FENTANYL should never be given to anyone other than the individual for whom it was prescribed because of the risk of death or other serious medical problems to that person for whom it was not intended.

22. Patients should be instructed to keep TEVA-FENTANYL in a secure place out of the reach of children due to the high risk of fatal respiratory depression.

23. When TEVA-FENTANYL is no longer needed, the unused patches should be removed from their pouches, folded so that the adhesive side of the patch adheres to itself, and returned to a pharmacy for proper disposal.

24. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with TEVA-FENTANYL.

25. Patients should be informed that accidental exposure or misuse may lead to death or other serious medical problems.

26. Patients should be informed that, if the patch dislodges and accidentally sticks to the skin of another person, they should immediately take the patch off, wash the exposed area with water and seek immediate medical attention for the accidentally exposed individual.

Special Populations

Pregnant Women: Fentanyl has been shown to impair fertility and to have an embryocidal effect in rats when given in intravenous doses 0.3 times the human dose for a period of 12 days. No evidence of teratogenic effects has been observed after the administration of fentanyl to rats.

The safe use of fentanyl has not been established with respect to possible adverse effects upon human fetal development. Therefore, TEVA-FENTANYL should not be used in women of childbearing potential unless, in the judgement of the physician, the potential benefits outweigh the possible hazards. Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**).

Use of TEVA-FENTANYL is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Use of TEVA-FENTANYL during childbirth is contraindicated because fentanyl passes through the placenta and may cause respiratory depression in the newborn child.

Nursing Women: Fentanyl is excreted in human milk, therefore TEVA-FENTANYL is contraindicated for use in nursing women because of the possibility of effects in their infants. Life-threatening respiratory depression may occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if TEVA-FENTANYL is used in this population.

Pediatrics (<18 years of age): The use of TEVA-FENTANYL in children under 18 years of age is not recommended, as the safety and efficacy of fentanyl transdermal systems have not been studied in the pediatric population. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal system.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see **DOSAGE AND ADMINISTRATION**). Therefore, it may be appropriate, according to clinical judgment, to initiate these patients on a lower TEVA-FENTANYL dose than that which the conversion tables recommend, including the use of the 12 mcg/h dose by itself or in combination with another dose, provided the patient is not opioid-naive (see **CONTRAINDICATIONS**). The 12 mcg/h strength may also be used for dose titration up or down, as using small increments for dose adjustment is recommended to enhance tolerability of opioid therapy (see **DOSAGE AND ADMINISTRATION**). As with all TEVA-FENTANYL patients, they should be carefully monitored for pain levels and adverse events, particularly hypoventilation.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Cancer Trials – Adults

Open-Label and Active-Control Double-Blind Studies

The safety of fentanyl transdermal system has been evaluated in 153 cancer patients and 357 post-operative patients. The duration of fentanyl transdermal system use varied in cancer patients: 56% of patients used fentanyl transdermal system for over 30 days, 28% continued treatment for more than 4 months, and 10% used fentanyl transdermal system for more than 1 year. In cancer patients, fentanyl transdermal system was administered in doses of 25 mcg/h to 600 mcg/h. Patients with acute pain used fentanyl transdermal system for 1 to 3 days.

Respiratory depression, the most serious adverse reaction, was observed in 3 (2%) of the cancer patients and 13 (4%) of post-operative patients. Hypotension and hypertension were observed in 11 (3%) and 4 (1%) of the opioid-naive patients.

Placebo-Controlled Study

Adverse events occurring at a greater frequency than placebo were identified in a placebo-controlled clinical trial of fentanyl transdermal system (25 mcg/h to 100 mcg/h) in cancer patients. Patients were stabilized on morphine for 7 days, and those who achieved adequate pain relief (n=131) were then switched to fentanyl transdermal system. During the initial open-label dose-titration and stabilization period of 15 days, a total of 43 patients dropped out; four experienced dyspnea, 3 nausea and 1 severe hallucinations.

Following this stabilization period, the nine-day double-blind period began, with patients randomized to either continue the dose of fentanyl transdermal system achieved during stabilization (n=47) or to switch to placebo (n=48). Rescue morphine was available. The median dose of fentanyl transdermal system was 50 mcg/h. Adverse events during this period, as reported by at least 1 fentanyl transdermal system patient (2.1%), and with a higher frequency of occurrence versus placebo include: vomiting (4.3% vs 0%), and the following events at 2.1% vs 0%: abscess, vertigo, hemorrhage, abdominal pain and jaundice.

Chronic Non-Cancer Pain Trials - Adults

The safety findings from the two primary trials (FEN-INT-12, n=248 patients; and FEN-INT-13, n=532 patients) are described below (see **Product Monograph, Part II: CLINICAL TRIALS,** Chronic Non-Cancer Pain (CNCP) Trials for methodological details on the trials).

Safety Findings

Adverse events related to respiratory depression (reported as either bradypnea or hypoventilation) have been reported in 3/780 (0.4%) of the CNCP patients, leading to discontinuation in all three cases.

There were nine deaths (all in the one-year trial): four were due to cardiac events, three to pneumonia, one to a cerebrovascular event, and one to cancer.

The discontinuation rates were 16% for the one-month crossover trial (FEN-INT-12) and 43% for the one-year trial (FEN-INT-13).

Of the 780 patients, 149 (19%) received less than one month fentanyl transdermal system treatment, 272 (35%) used fentanyl transdermal system for one to six months, 137 (18%) for six months to one year and 222 patients (28%) continued treatment for more than one year.

Among patients who completed the one-year trial (n=301 of 530 ITT patients), the mean dose at the 12-month endpoint was 90.4 mcg/h, with the most common dose being 75 mcg/h.

Most Common Adverse Events

A causal relationship of adverse events to fentanyl transdermal system was not always determined. The most commonly observed adverse events in the non-cancer chronic pain clinical trials, regardless of causal relationship, are: nausea or vomiting, somnolence, constipation, sweating, headache, dizziness, pruritus and depression.

Other reported adverse reactions occurring in > 1% of patients that are probably or likely related to fentanyl transdermal system treatment are:
Application Site: application site reaction
Body as a Whole: fatigue, pain, malaise, asthenia, hot flushes, withdrawal syndrome, back pain, rigors, temperature changed sensation
Central and Peripheral Nervous System: tremor, vertigo, hypertonia
Gastrointestinal System: dry mouth, diarrhea, abdominal pain, dyspepsia
Heart Rate and Rhythm: palpitation
Liver and Biliary System: hepatic enzymes increased, gamma-GT increased
Metabolic and Nutritional: weight decreased, LDH increased
Psychiatric: anorexia, anxiety, confusion, insomnia, nervousness, agitation, hallucination, concentration impaired, emotional lability, amnesia
Respiratory System: dyspnea
Skin and Appendages: rash erythematous, skin disorder

Chronic Pain Trials - Pediatrics

The safety of fentanyl transdermal system has been evaluated in 293 opioid-tolerant pediatric patients (age 18 years or less) with chronic pain, with n=63 receiving fentanyl transdermal system for at least 2 months. Approximately 60% of the patients had underlying pain due to malignancy. The number of patients in the lower age ranges were as follows: n=2 patients < 2 years old; n=65 patients 2 to < 6 years old; n=100 patients 6 to <12 years old. The most commonly reported adverse events regardless of causality include: vomiting (14.3%), nausea (11.6%), constipation (9.2%), pruritus (8.2%), and somnolence (5.8%). Three patients experienced respiratory depression within 96 hours of beginning fentanyl transdermal system; two of these patients died. The underlying condition of the patients contributed to the deaths. The third patient's decreased respiratory rate was resolved after temporary discontinuation of fentanyl transdermal system.

Dosing recommendations for the safe and effective use of fentanyl transdermal systems in this patient population have not been established, in view of the combination of:

i) the variety of factors which could lead to overexposure from fentanyl transdermal systems in children as compared to adults (including smaller body weight and significantly different body surface area; differential skin characteristics; potential for magnification, compared to adults, of the impact of amount of body fat stores, muscle wasting, fever, external heat), and
ii) the limitations in both formal PK data (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**) and exposure data (as above).

Post-Market Adverse Drug Reactions

In post-marketing experience, deaths from hypoventilation have been reported in cases of inappropriate use of fentanyl transdermal system. Other respiratory events associated with the use of fentanyl transdermal system include apnea, sleep apnea syndrome, respiratory distress and hypoxia.

Other opioid-related adverse reactions include: nausea, vomiting, constipation, ileus or subileus, upper abdominal pain, hypotension, bradycardia, cyanosis, miosis, somnolence, headache, confusion, disorientation, hallucination, euphoria, depressed level of consciousness or loss of consciousness, blurred vision, pruritus, sweating, pyrexia, influenza like illness, tachycardia, hypoesthesia, paresthesia, peripheral edema, muscle spasms or muscle twitching, sexual dysfunction, erectile dysfunction, and urinary retention.

Skin reactions such as rash, erythema and itching have occasionally been reported. These reactions usually resolve within 24 hours or upon removal of the patch. Other skin reactions such as application site hypersensitivity, application site erosion, application site ulcer, dermatitis, allergic dermatitis, contact dermatitis, and eczema have also been reported.

Hypersensitivity has been reported following use of fentanyl transdermal system. There have also been very rare reports of anaphylactic and anaphylactoid reaction, including Stevens-Johnson syndrome, airway constriction, swelling, anaphylactic shock, and two deaths that occurred within 24 hours of the anaphylactic reaction. In one case, it was the care-giver of the patient who experienced dyspnea, urticaria and swelling, within ten minutes of applying the patch to the patient.

There have also been rare reports of convulsions, including clonic convulsions and grand mal convulsions. In two cases, vegetative state or coma was reported to immediately follow the convulsions.

Opioid withdrawal symptoms, such as nausea, vomiting, diarrhea, anxiety and shivering are possible in some patients after conversion from their previous opioid analgesic to TEVA-FENTANYL or if therapy is stopped suddenly. There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used fentanyl

transdermal systems during pregnancy (see **WARNINGS AND PRECAUTIONS: Special Populations, Pregnant Women**).

Post-marketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome following the concomitant use of fentanyl with a serotonergic drug, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) (see **WARNINGS AND PRECAUTIONS, Neurologic** and **DRUG INTERACTIONS, Drug-Drug Interactions**).

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Drug-Drug Interactions

Based on its pharmacodynamic and pharmacokinetic properties, fentanyl exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations, and lists of examples are described below. These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is coadministered with fentanyl be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to coadministration.

Overview

Interactions with Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol):

TEVA-FENTANYL (fentanyl) should be dosed with caution in patients who are currently taking other CNS depressants or other drugs that may cause respiratory depression, hypotension, profound sedation, or may potentially result in coma. Such agents include antidepressants, antihistamines, antipsychotics, anxiolytics, barbiturates, benzodiazepines, centrally acting antiemetics, chloral hydrate, clonidine and related substances, general anaesthetics, some heart medications (e.g. beta-blockers), neuroleptics, other opioid derivatives (analgesic and antitussive) phenothiazines and sedatives or hypnotics. When such combined therapy is contemplated, a substantial reduction in dose of one or both agents should be considered and patients carefully monitored. Patients should also be warned that these combinations increase central nervous system depression and can make driving vehicles and operating machinery hazardous (see **WARNINGS AND PRECAUTIONS, Psychomotor Impairment**). TEVA-FENTANYL should not be consumed with alcohol as it may increase chance of experiencing dangerous side effects.

CYP 3A4 Inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore, potential interactions may occur when fentanyl transdermal system is given concurrently with agents that affect CYP3A4 activity. The concomitant use of transdermal fentanyl with ritonavir or other potent 3A4 inhibitors such as ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, voriconazole, erythomycin and grapefruit juice may result in an increase in fentanyl plasma concentrations which could increase or prolong adverse drug effects and may cause serious respiratory depression (see also **WARNINGS AND PRECAUTIONS, Concomitant Use of CYP3A4 Inhibitors**). In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and TEVA-FENTANYL is not recommended, unless the patient is closely monitored.

CYP 3A4 Inducers
Coadministration with agents that induce 3A4 activity such as rifampicin, carbamazepine, phenobarbital, phenytoin may reduce the efficacy of fentanyl transdermal system. This may require a dose adjustment of TEVA-FENTANYL. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and may result in an increase in fentanyl plasma concentration which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression.

MAO Inhibitors
Severe and unpredictable potentiation by MAO inhibitors (MAOIs) has been reported with opioid analgesics. MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). TEVA-FENTANYL is contraindicated in patients taking MAOIs (e.g., phenelzine, tranylcypromine, linezolid) or within 14 days of stopping treatment. (see **CONTRAINDICATIONS**).

Serotonergic Drugs
Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition. Use concomitantly with caution. Carefully observe the patient, particularly during treatment initiation and dose adjustment (see **WARNINGS AND PRECAUTIONS, Neurologic** and **ADVERSE REACTIONS, Post- Market Adverse Drug Reactions**).

Interaction with Mixed Agonist/Antagonist Analgesics: The concomitant use of TEVA-FENTANYL with mixed agonist/antagonist analgesics (e.g., buprenorphine, butorphanol, 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 (see **WARNINGS AND PRECAUTIONS, Dependence/Tolerance**).

Muscle Relaxants
Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and

produce an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of TEVA-FENTANYL and/or the muscle relaxant as necessary.

Diuretics
Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs
The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when TEVA-FENTANYL is used concomitantly with anticholinergic drugs.

Drug-Lifestyle Interaction
The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, Neurologic**).

DOSAGE AND ADMINISTRATION

General
TEVA-FENTANYL should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

TEVA-FENTANYL should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for treatment of pain and in the detection and management of respiratory depression including the use of opioid antagonists.

At the time of the switch to TEVA-FENTANYL from other opioids, patients must be tolerant to opioid therapy of comparable potency to that of the intended initiating dose. Use of TEVA-FENTANYL in patients who are non-opioid-tolerant, or insufficiently tolerant, may lead to fatal respiratory depression.

Placing TEVA-FENTANYL patch in mouth, chewing it, swallowing it or using it in any ways other than indicated may cause choking or overdose that could result in death (see SERIOUS WARNINGS AND PRECAUTIONS Box).

Dosing Considerations
TEVA-FENTANYL doses must be individualized based upon the status of each patient and should be assessed at regular intervals after application. Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest effective dose of TEVA-FENTANYL which will achieve the overall treatment goal of satisfactory pain

relief with acceptable side effects. Dosage of the drug must be individualized according to the response and tolerance of the patient. The most important factor to be considered in determining the appropriate dose is the extent of pre-existing opioid tolerance. Reduced doses of TEVA-FENTANYL are suggested for the elderly and other groups discussed in **WARNINGS AND PRECAUTIONS**.

There has been no systematic evaluation of fentanyl transdermal systems as an initial opioid analgesic in the management of chronic pain. Most patients in the clinical trials were converted to fentanyl transdermal system from other opioid therapies on which inadequate to moderate pain control had been experienced prior to conversion.

Initiation of TEVA-FENTANYL in patients who are opioid-naïve is contraindicated at any dose (see CONTRAINDICATIONS). The initial dose of TEVA-FENTANYL should be obtained from the conversion tables in DOSAGE AND ADMINISTRATION, and must <u>not</u> be higher than that dose which is equivalent to the total dose of opioids the patient is receiving at the time of the switch to the patch. It may be appropriate, according to clinical judgment, to initiate some patients on a lower TEVA-FENTANYL dose than that which the conversion tables recommend, including the use of the 12 mcg/h dose by itself or in combination with another dose, provided the patient is not opioid-naive (see CONTRAINDICATIONS).

In general the 12 mcg/h dose, which allows for smaller dose increases than does the 25 mcg/h patch, is to be used for titration/adjustments of dosage (for oral morphine equivalency in dose adjustment, see Recommended Dose and Dose Adjustment; <u>Dose Adjustment</u>; and Titration Dose Increment). The 12 mcg/h dose is not included in the conversion tables (Tables 1.1 and 1.2) because it is generally not to be used as the initiating dose.

Opioid analgesics may be only partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with these types of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

TEVA-FENTANYL has a high potential for abuse and diversion (see WARNINGS AND PRECAUTIONS).

<u>Concomitant Use of CYP3A4 Inhibitors</u>

The concomitant use of TEVA-FENTANYL with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients concomitantly exposed to TEVA-FENTANYL and potent CYP3A4 inhibitors should be carefully monitored for an extended period of time and dosage adjustments should be made if warranted (**see DRUG INTERACTIONS**).

Recommended Dose and Dosage Adjustment

Pediatrics
The use of TEVA-FENTANYL in children under 18 years of age is not recommended as the safety and efficacy of fentanyl transdermal system have not been studied in the pediatric population. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal system.

Adults: Initial Dose Selection
In selecting an initial TEVA-FENTANYL dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g. whether it is a pure agonist or mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the TEVA-FENTANYL dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, and 4) the general condition and medical status of the patient.

At the time of the switch to TEVA-FENTANYL, patients must be tolerant to opioid therapy of comparable potency to that of the intended initiating dose. It may be appropriate, according to clinical judgment, to initiate some patients on a lower TEVA-FENTANYL dose than that which the conversion tables recommend, which may include use of the 12 mcg/h dose. The 12 mcg/h dose is not included in the conversion tables (Tables 1.1 and 1.2), because it is generally to be used for dose adjustment rather than as the initiation dose, except in the case of patients who, because of their clinical status, are to be initiated on a lower dose than that which the conversion tables recommend. Overestimating the TEVA-FENTANYL dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Due to the mean elimination half-life of 20 hours of fentanyl transdermal system, patients who are thought to have had a serious adverse event, including overdose, will require monitoring and treatment for at least 24 hours or until the adverse event has subsided.

Parenteral/Oral/Equianalgesic Potency Conversion
To convert adult patients from oral or parenteral opioids to TEVA-FENTANYL, use Table 1.1.

Alternatively, for adult patients taking opioids or doses not listed in Table 1.1, use the following methodology:
1. Calculate the previous 24-hour analgesic requirement expressed in morphine equivalents.
2. Use Table 1.2 to convert this equianalgesic morphine dose to the recommended initial TEVA-FENTANYL dose. **This conversion recommendation is intentionally conservative to minimize the potential for TEVA-FENTANYL overdosage.**

For delivery rates in excess of 100 mcg/h, multiple systems may be applied.

Because of the gradual increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of TEVA-FENTANYL cannot be made before 24 hours of wearing. Patients should use short-acting

analgesics after the initial dose application as needed until analgesic efficacy with TEVA-FENTANYL is attained.

Initial Dose Selection in Elderly, Cachectic, or Debilitated Patients
In patients from these populations, fentanyl transdermal system may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance. Therefore, it may be appropriate, according to clinical judgment, to initiate these patients on TEVA-FENTANYL at a dose level lower than that which the conversion tables recommend, including the use of the 12 mcg/h dose by itself or in combination with another dose, provided the patient is not opioid-naive (see **CONTRAINDICATIONS**). As with all TEVA-FENTANYL patients, they should be carefully monitored for pain levels and adverse events, particularly hypoventilation.

Dose Adjustment
Dose titration is the key to success with opioid analgesic therapy. The recommended initial TEVA-FENTANYL dose based upon the daily morphine dose is conservative, and 50% of patients are likely to require a dose increase after initial application of TEVA-FENTANYL. If analgesia is insufficient after the initial application, the first dosage increase should occur three days after application, while all subsequent dosage increases should occur six days following the previous application.

Initial Dosage Increase: The initial TEVA-FENTANYL dosage may be increased after 3 days based on the daily dose of supplemental analgesics required by the patients in the second or third day of the initial application.

All Other Dosage Increases: Physicians are advised that it may take up to 6 days after increasing the dose of TEVA-FENTANYL for the patient to reach equilibrium on the new dose. Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Titration Dose Increment: Dosage of TEVA-FENTANYL must be individualized according to the pain relief and tolerance of the patient. Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 45-59 mg/24 hours of oral morphine to a 12 mcg/h increase in TEVA-FENTANYL dose. For example, if at the end of the required 6-day duration with a new patch strength, a patient is consuming an average daily dose of 150 mg of oral morphine, then the recommended TEVA-FENTANYL dose increase would be 3x12 mcg/h, which can be achieved by three 12 mcg/h patches, or one of 25 mcg/h and one of 12 mcg/h. The use of 12 mcg/h in the ratio for calculation of TEVA-FENTANYL dose increases allows for achieving smaller increments when needed, i.e. increments that are as close as possible to the actual average amount of supplementary oral morphine. Some patients may continue to require periodic supplemental doses of short-acting analgesic for "breakthrough" pain.

Maintenance

The majority of patients are adequately maintained with TEVA-FENTANYL administered every 72 hours. A small number of patients may not achieve adequate analgesia using this dosing interval and may require systems to be applied every 48 hours rather than every 72 hours. If breakthrough pain repeatedly occurs at the end of the dosing interval, it is generally an indication for a dosage increase rather than more frequent administration. An increase in the **TEVA-FENTANYL** dose should be considered before changing dosing intervals in order to maintain patients on a 72-hour regimen.

Some patients may require additional or alternative methods of opioid administration when the TEVA-FENTANYL dose exceeds 300 mcg/h.

Decreased Dosing or Discontinuation of TEVA-FENTANYL

Following the successful relief of severe pain, periodic attempts should be made to reduce the opioid dose. Lower doses or complete discontinuation of the opioid analgesic may become feasible due to physiological change or improved mental state of the patient.

For all downward titration, it is important to note that it takes 20 hours or more for the fentanyl serum concentration to fall by 50% after system removal.

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including TEVA-FENTANYL. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

There have been reports that rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms and uncontrolled pain.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualized and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Safe Use of Tables 1.1 and 1.2

To convert patients to another opioid, remove TEVA-FENTANYL and titrate the dose of the new analgesic, based upon the patient's report of pain, until adequate analgesia has been attained.

Tables 1.1, and 1.2 should not be used to convert from TEVA-FENTANYL to other opioid therapies. Because the conversion to TEVA-FENTANYL is conservative, use of Tables 1.1, and 1.2 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.

Table 1.1[1]: Dose Conversion Guidelines

Dose Conversion Guidelines are Unidirectional and for Chronic Use.
Use this table to convert patients from the Current Analgesic ONLY to TEVA-FENTANYL.
Do NOT use this table to convert patients from TEVA-FENTANYL to other opioids; doing so may result in overdose and toxicity.

Current Analgesic	Daily Dosage (mg/d)						
Oral morphine	60-134	135-179	180-224	225-269	270-314	315-359	360-404
IM/IV morphine (based on a 1:3 IM:PO ratio)	20-44	45-60	61-75	76-90	NA[2]	NA[2]	NA[2]
Oral oxycodone	30-66	67-90	91-112	113-134	135-157	158-179	180-202
Oral codeine	150-447	448-597	598-747	748-897	898-1047	1048-1197	1198-1347
Oral hydromorphone	8-16	17-22	23-28	29-33	34-39	40-45	46-51
IV hydromorphone[3]	4.0-8.4	8.5-11.4	11.5-14.4	14.5-16.5	16.6-19.5	19.6-22.5	22.6-25.5
	↓	↓	↓	↓	↓	↓	↓
TEVA-FENTANYL Dose	**25 mcg/h**	**37 mcg/h**	**50 mcg/h**	**62 mcg/h**	**75 mcg/h**	**87 mcg/h**	**100 mcg/h**

[1]Table 1.1 should not be used to convert from TEVA-FENTANYL to other therapies because this conversion to TEVA-FENTANYL is conservative. Use of Table 1.1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible (see DOSAGE AND ADMINISTRATION, Safe Use of Tables 1.1 and 1.2.)

[2] NA reflects insufficient data available for guidance. Prescribers should make these conversions very carefully and conservatively.

[3]The conversion ratio of parenteral hydromorphone to oral hydromorphone of 1:2 is based on clinical experience in patients with chronic pain. Reference: Parenteral Drug Therapy Manual, Vancouver General Hospital, Pharmaceutical Sciences Clinical Services.

Table 1.2[#]

Recommended Initial TEVA-FENTANYL Dose Based upon Daily Oral Morphine Dose[‡]

Oral 24-hour morphine (mg/day)		TEVA-FENTANYL Dose (mcg/h)
Dose Adjustment	45-59	12
Initiation Dose	60-134	25
	135-179	25+12
	180-224	50
	225-269	50+12
	270-314	75
	315-359	75+12
	360-404	100
	405-494	125
	495-584	150
	585-674	175
	675-764	200
	765-854	225
	855-944	250
	945-1034	275
	1035-1124	300

[‡] In clinical trials these ranges of chronic daily oral morphine doses were used as a basis for conversion to fentanyl transdermal system. See **Recommended Dose and Dosage Adjustment.** **and** **Dose Adjustment**.

[#]12 mcg/h dose is included in this table for dose adjustment. 12 mcg/h dose generally should not be used as the initiating dose, except in the case of patients for whom clinical judgment deems it appropriate to start TEVA-FENTANYL at less than 25 mcg/h; TEVA-FENTANYL at any dose is contraindicated in opioid-naive patients (see **CONTRAINDICATIONS**).

Administration

Application of TEVA-FENTANYL Patch

TEVA-FENTANYL should be applied to non-irritated and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. Hair at the application site should be clipped (not shaved) prior to application. If the site of TEVA-FENTANYL application must be cleansed prior to application of the system, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that may irritate the skin or alter its characteristics. Allow the skin to dry completely prior to system application.

TEVA-FENTANYL should be applied immediately upon removal from the sealed package. The system should not be altered, e.g. cut in any way prior to its application. The transdermal system should be pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.

Each TEVA-FENTANYL system may be worn continuously for 72 hours. A new system should be applied on a different skin site after removal of the previous transdermal system.

Disposal of TEVA-FENTANYL Patch
TEVA-FENTANYL should be kept in a safe place, out of the sight and reach of children before, during and after use. TEVA-FENTANYL should not be used in front of children, since they may copy these actions.

Upon removal, the used patch should be folded in half so that the adhesive side of the patch adheres to itself, and should be immediately packaged in such a way as to prevent accidental exposure to others, including children or pets until it can be returned to a pharmacy for proper disposal. If the drug adhesive layer accidentally contacts the skin, the area should be washed with clear water. Do not use soap, alcohol or other solvents as these may enhance the drug's ability to penetrate the skin. Used patches still contain a considerable amount of drug. Unused patches should be removed from their pouch, folded so that the adhesive side of the patch adheres to itself, and disposed of similarly to used patches. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

TEVA-FENTANYL should never be disposed of in household trash.
Disposal via a pharmacy take-back program is recommended.

OVERDOSAGE

Symptoms
The manifestations of fentanyl overdosage are an extension of its pharmacologic actions with the most serious effect being respiratory depression.

Treatment
For management of respiratory depression, immediate countermeasures include removing TEVA-FENTANYL and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. Following removal of the fentanyl transdermal system, serum concentrations of fentanyl decline slowly, with a mean half-life of 20 hours. Due to this the duration of respiratory depression following an overdose may be longer than the effects of the opioid antagonist's action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the opioid effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, establish and maintain a patent airway, administer oxygen and assist or control respiration as indicated, and use an oropharyngeal airway or endotracheal tube if necessary. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolemia should be considered, and managed with appropriate parenteral fluid therapy.

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Fentanyl is an opioid analgesic which interacts predominantly with the μ-opioid receptor. Fentanyl produces analgesia, sedation, respiratory depression, constipation, and physical dependence but appears to have less emetic activity than other opioid analgesics. Fentanyl may produce muscle rigidity, miosis, cough reflex suppression, alterations in mood, bradycardia and bronchoconstriction.

Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

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

At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in man indicate that histamine release rarely occurs with fentanyl. Assays in man show no clinically significant histamine release in dosages up to 50 mcg/kg.

Both the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

Pharmacokinetics

Fentanyl transdermal systemprovides continuous systemic delivery of fentanyl for up to 72 hours. Fentanyl is released along the concentration gradient existing between the drug adhesive layer of the system and the lower concentration in the skin.

Adults

Fentanyl transdermal system

Absorption:
Fentanyl is released at a relatively constant rate. The concentration gradient existing between the matrix and the lower concentration in the skin drives drug release. Following initial fentanyl transdermal system administration, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours and remaining relatively constant for the remainder of the 72-hour application period. Peak serum levels of fentanyl generally occur between 24 and 72 hours after the first application. The AUC and C_{max} over a dosing interval at a steady state are approximately 40% higher than a single application.

Serum fentanyl concentrations achieved are proportional to the fentanyl transdermal system delivery rate (see Table 1.3). With continuous use, serum fentanyl concentrations continue to rise for the first few system applications. After several sequential 72-hour applications, patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl.

Table 1.3:
Pharmacokinetic Parameters of TTS (fentanyl) in Adults

	Mean (SD) Maximal Concentration C_{max} (ng/mL)	**Mean (SD) Time to Maximal Concentration T_{max} (h)**
Fentanyl transdermal system 12 mcg/h	0.3 (0.2)	27.5 (9.6)
Fentanyl transdermal system 25 mcg/h	0.6 (0.3)	38.1 (18.0)
Fentanyl transdermal system 50 mcg/h	1.4 (0.5)	34.8 (15.4)
Fentanyl transdermal system 75 mcg/h	1.7 (0.7)	33.5 (14.5)
Fentanyl transdermal system 100 mcg/h	2.5 (1.2)	36.8 (15.7)

After fentanyl transdermal system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20 (range 20-27) hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life ranges from 3-12 hours.

Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see **WARNINGS AND PRECAUTIONS, Risk of Unintentional Increase in Drug Exposure**). An increase in skin temperature through the application of a heating pad on low setting over the fentanyl transdermal system during the first 10 hours of a single application increased the mean fentanyl AUC value by 2.2-fold and the mean concentration at the end of heat application by 61%.

Distribution:

Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3 to 10 L/kg after intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is released slowly into blood. Plasma protein binding of fentanyl has been reported to be approximately 84% in healthy subjects. In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%). Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Metabolism:

Skin does not appear to metabolize fentanyl delivered transdermally. Fentanyl is metabolized primarily in the liver. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation. In humans, the drug is metabolized primarily by N-dealkylation to norfentanyl and other inactive metabolites.

Excretion:

Within 72 hours of IV fentanyl administration, approximately 75% of the fentanyl dose is excreted in urine, mostly as metabolites, with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.

Special Populations and Conditions

Pediatrics Under 18 Years of Age: Fentanyl transdermal system was not studied in children under 2 years of age. Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied fentanyl patches in the dose range of 12 to 300 mcg/hour. Adjusting for body weight, clearance (L/h/kg) appears to be approximately 80% higher in children 2 to 5 years old and 25% higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are expected to have a similar clearance as adults.

Dosing recommendations for the safe and effective use of fentanyl transdermal system in this patient population have not been established, in view of the combination of:

i) the variety of factors which could lead to overexposure from fentanyl transdermal system in children as compared to adults (including smaller body weight and significantly different body surface area; differential skin characteristics; potential for magnification, compared to adults, of the impact of amount of body fat stores, muscle wasting, fever, external heat), and
ii) the limitations in both formal PK data (as above) and exposure data (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Chronic Pain Trials - Pediatrics)**

Elderly or Debilitated Patients: In elderly, cachectic, or debilitated patients, fentanyl transdermal system may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance. The clearance of fentanyl may be reduced, and the terminal half-life prolonged (see **DOSAGE AND ADMINISTRATION**).

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger

patients. In a study conducted with fentanyl transdermal system healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 mcg/h application of fentanyl transdermal system were assessed. Although t_{max} and $t_{1/2}$ were not altered, the mean plasma C_{max} and AUC values increased by approximately 35% and 73%, respectively, in these patients. Based on a population pharmacokinetic model, simulated data in patients with different grades of impaired liver function treated with transdermal fentanyl suggest that the steady-state AUC of patients with Grade B (Child-Pugh Score = 8) and Grade C (Child- Pugh Score = 12.5) liver disease would be approximately 1.36 and 3.72 times larger, respectively, compared with patients with normal liver function (Grade A [Child-Pugh Score 5.5]).

Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of TEVA-FENTANYL reduced if necessary.

Renal Impairment: Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive TEVA-FENTANYL, they should be observed carefully for signs of fentanyl toxicity and the dose should be reduced if necessary.

STORAGE AND STABILITY

TEVA-FENTANYL is stable for 2 years from date of manufacturing when stored in sealed pouch between 15° and 25 °C. Do not refrigerate or freeze.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store TEVA-FENTANYL securely, in a location not accessible by others. Keep out of the sight and reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

TEVA-FENTANYL should be kept in a safe place, out of the sight and reach of children before, during and after use.

Do not cut TEVA-FENTANYL patches.

Upon removal, the used patch should be folded in half so that the adhesive side of the patch adheres to itself, and should be immediately packaged in such a way as to prevent accidental exposure to others, including children or pets until it can be returned to a pharmacy for proper

disposal. If the drug adhesive layer accidentally contacts the skin, the area should be washed with clear water. Do not use soap, alcohol or other solvents as these may enhance the drug's ability to penetrate the skin. Used patches still contain a considerable amount of drug. Unused patches should be removed from their pouch, folded so that the adhesive side of the patch adheres to itself, and disposed of similarly to used patches. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

Wash hands, with water only, after applying or removing the patch.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-FENTANYL is a transdermal patch providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.

TEVA-FENTANYL is a rectangular unit comprising a release liner, adhesive drug containing matrix, and a backing. Proceeding from the outer surface toward the surface adhering to the skin, TEVA-FENTANYL is made up of: 1) a backing made of foil which is in contact with the self-adhesive drug containing matrix, 2) a self-adhesive drug containing the matrix of, Polybutyltitanate, and Duro-Tak®. 3) A peelable release liner covering the adhesive layer must be removed before the system can be applied. The protective liner comprises Polyethyleneterepthalate (siliconized on the one side in contact with the matrix) and is printed with blue ink.

TEVA-FENTANYL is available in five different strengths. Each system is labelled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin. The active component of the system is fentanyl. The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/h per 7.5 cm^2). The 3.75, 7.5, 15, 22.5 and 30 cm^2 systems are designed to deliver 12.5, 25, 50, 75 or 100 mcg/h fentanyl to the systemic circulation, representing approximately 0.3, 0.6, 1.2, 1.8 or 2.4 mg per day, respectively. The remaining components are pharmacologically inactive.

Total fentanyl contents and system sizes for the five strengths are summarized below:

Table 1.4

System	Nominal fentanyl delivery rate (mcg/h)	Total fentanyl content (mg)	System size (cm^2)	System dimensions (without release liner)	Print in blue ink on backing film (outside layer of system)
TEVA-FENTANYL 12	12.5	2.063	3.75	20 x 20 mm	"fentanyl 12 mcg/h"
TEVA-FENTANYL 25	25	4.125	7.5	30 x 26mm	"fentanyl 25 mcg/h"
TEVA-FENTANYL 50	50	8.25	15	30 x 51mm	"fentanyl 50 mcg/h"

TEVA-FENTANYL 75	75	12.375	22.5	47.5 x 48mm	"fentanyl 75 mcg/h"
TEVA-FENTANYL 100	100	16.5	30	47.5 x 64mm	"fentanyl 100 mcg/h"

TEVA-FENTANYL is supplied in cartons containing 5 individually packaged systems.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

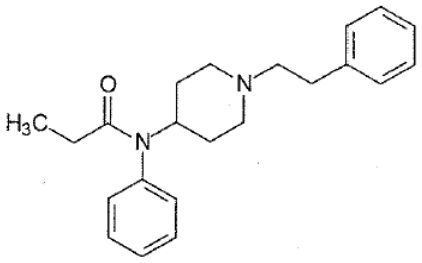
Drug Substance

Proper name: fentanyl base

Chemical name: N-phenyl-N-(1 -2-phenylethyl-4-piperidyl)propanamide

Molecular formula and molecular mass: $C_{22}H_{28}N_2O$, 336.46 g/mol

Structural formula:



Physicochemical properties: Fentanyl base is a white or slightly creamy white crystalline powder with a melting range of 84°-86°C. It is very slightly soluble in water (0.16 mg/mL), slightly soluble in a neutral buffer (1.2 mg/mL), freely soluble in ethanol, acetonitrile and methylene chloride. The n-octanol:water partition coefficient is 860:1. The pKa is 8.4.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDIES

A single center, randomized, two-way crossover, comparative bioequivalence study, after a single dose application, was conducted on 32 healthy volunteers of both genders (15 female and 17 male). The transdermal system remained applied for 72 hours. TEVA-FENTANYL 100 mcg/h, by Teva Canada Ltd. was compared to Duragesic® 100 mcg/h, by Janssen-Ortho Inc., Canada. The results show that TEVA-FENTANYL is bioequivalent to Duragesic®. The results are tabulated in Table 2.

Table 2

Fentanyl Transdermal System (1 x 100mcg/h for 72 hours patch application) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{72} (h*pg/mL)	94191.75 98152.05 (28.28)	94854.95 99137.98 (31.11)	99.3	93.05-105.97
AUC_T (h*pg/mL)	129143.89 135472.94 (31.05)	130625.78 137782.55 (34.81)	98.84	93.05-105.00
AUC_I (h*pg/mL)	133502.70 140520.61 (32.39)	135174.97 143361.85 (36.85)	98.76	92.98-104.90
C_{max} (pg/mL)	1965.97 2038.18 (26.64)	2091.69 2165.37 (27.78)	93.99	86.71-101.88
T_{max}§ (h)	37.1 (49.46)	36.1 (41.27)		
$T_{½}$□ (h)	21.76 (22.67)	22.20 (24.95)		

* TEVA-FENTANYL,Teva Canada Ltd..

† Duragesic®, is manufactured by Janssen-Ortho Inc., Canada, and was purchased in Canada

§ Expressed as the arithmetic mean (CV%) only

□ Expressed as the arithmetic mean (CV%) only

Fentanyl transdermal system

Cancer Trials-Adults

During the pre-marketing phase, clinical trials were conducted in 153 patients to evaluate the efficacy and safety of fentanyl transdermal system therapy for pain due to cancer. The studies were open-labelled with the exception of one trial which incorporated a randomized, double-blind crossover component (fentanyl transdermal system therapy versus placebo) in 46 patients. Doses in these studies varied between 25 and 600 mcg/h. Patients used fentanyl

transdermal system continuously for up to 866 days; 56% received fentanyl transdermal therapy for over 30 days, 28% continued treatment for more than 4 months and 10% used fentanyl transdermal therapy for more than 1 year. The results of these studies demonstrated that: 1) satisfactory analgesia was achieved in the majority of patients and, 2) fentanyl transdermal therapy was accepted by cancer patients, their caregivers and physicians.

Since the introduction of fentanyl transdermal therapy, additional trials have been conducted in approximately 350 chronic cancer pain patients to confirm earlier conclusions. In the largest of these, a Canadian post-marketing surveillance study in 199 patients, a reduction in pain intensity and improved pain relief and well-being were observed in the 127 patients evaluable for efficacy. Patient preference for fentanyl transdermal therapy over their previous analgesic therapy was also observed. In these patients, the average treatment duration was 68 days (range: 17 - 118). The mean dose for all study patients increased from 51mcg/h at baseline to 128 mcg/h at the last dose on therapy.

Chronic Non-Cancer Pain (CNCP) Trials- Adults

The safety of fentanyl transdermal system has been evaluated in 908 patients with chronic pain conditions from a total of 5 trials. Pain conditions included low back pain, neuropathic pain and AIDS-associated pain. One of the two primary trials was an open-label single-arm one-year study with 530 patients (FEN-INT-13), and the other an open-label two-month crossover trial with 250 patients and slow release morphine as the comparator (FEN-INT-12). In both trials, neuropathic and nociceptive pain were present in 50% and 71% of the patients, respectively. The most frequent body regions causing pain were the lower back (43% of the patients) and lower limbs (22%); the body systems most frequently responsible for pain were the nervous (45%), and musculoskeletal systems and connective tissue (43%). The most common etiology was degenerative, mechanical (38%) or trauma (26%). Patients ranged from 22 to 88 years in age, with a median age of 49 years. Patients had experienced chronic pain for a median duration of six years, and reported at least moderate pain control over the preceding 7 days from a stable daily dose of opioids.

For more detail on the safety profiles from fentanyl transdermal system trials, see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions**.

DETAILED PHARMACOLOGY

Animal Pharmacology

Fentanyl exerts a typical opioid analgesic effect. Results were obtained in animal studies to define this activity.

Fentanyl was effective in the Haffner tail clamp test in mice, a test used to detect opioid analgesic activity. The ED_{50} for fentanyl was calculated to be 0.08 mg/kg s.c. and that for morphine, 15 mg/kg s.c. The onset of the analgesic effect occurred in 4 minutes with fentanyl and the duration was 30 minutes.

The compound exhibited activity in the tail-withdrawal test in rats, a test measuring the time

elapsing for a rat to remove its tail from a water bath heated to 55°C. Fentanyl was found to be 269 times more potent than morphine after subcutaneous administration and had a faster onset and shorter duration of action than the latter compound.

Fentanyl has been shown to produce analgesia in rabbits as evidenced by the failure of a painful stimulus applied to the trigeminal nerve to produce desynchronization of the EEG. Depression of the cortical activating system was evidenced by the increased cortical potentials seen after administration of fentanyl.

Low concentrations of fentanyl shifted the oxygen dissociation curve to the left, whereas high concentrations were ineffective.

Fentanyl, like other potent opioid analgesics, produces skeletal muscle rigidity. This muscular rigidity can be blocked or reversed by succinylcholine. Fentanyl has been demonstrated to have no effect on neuromuscular transmission in anesthetized cats.

The interaction of fentanyl with diazepam and pancuronium was investigated in the anesthetized dog. Fentanyl alone in a dose of 0.5 mg/kg IV decreased heart rate, cardiac output and arterial pressure in these animals. The administration of diazepam, 0.5 mg/kg IV after fentanyl caused some reversal of the decrease in heart rate and cardiac output. The subsequent administration of pancuronium completely reversed the decreased heart rate, cardiac output and arterial pressure. A decrease in cardiac output and arterial pressure leads to decreased pulmonary arterial pressure and blood flow.

Fentanyl was administered to anesthetized dogs in increasing dosages from 0.002 to 0.16 mg/kg IV. These doses caused no change in left ventricular pressure. Doses up to 0.03 mg/kg increased left ventricular maximum dp/dt, heart rate and cardiac afterload. Higher doses decreased pressure-time index and myocardial oxygen consumption by approximately 30%. Higher doses of fentanyl, administered rapidly, produced a fall in mean peripheral arterial pressure.

Moreover, other studies conducted in anesthetized dogs demonstrate that fentanyl decreases lactate production in the ischemic ventricle. This decrease in myocardial lactate production indicates that the compound decreased myocardial oxygen demand. Cardiovascular dynamics are not compromised in anesthetized dogs receiving large doses of fentanyl or fentanyl plus nitrous oxide.

In anesthetized cats, fentanyl produced a central sympatho-inhibitory effect, with the main site of action being the medulla oblongata.

Fentanyl, administered to isolated dog Purkinje and ventricular muscle fibres, was devoid of any action on cardiac transmembrane potentials.

When fentanyl was administered to anesthetized dogs with experimental coronary occlusion at a dose of 0.05 mg/kg IV, it markedly decreased heart rate, left ventricular maximum dp/dt and

cardiac output. These effects were reversed by the administration of atropine. Fentanyl was effective in preventing the occurrence of ventricular fibrillation in these animals.

Intra-arterial injections of fentanyl in anesthetized dogs in doses of 0.01 and 0.05 mg caused no change in femoral blood flow. Intra-arterial injection of 0.2 mg of fentanyl caused a decrease in vascular resistance indicating that higher doses of the compound possess a vasodilator component.

In anesthetized dogs, fentanyl significantly lowered pulmonary arterial pressure as well as pulmonary arterial driving pressure with little change in pulmonary vascular resistance and compliance. This reduction of pulmonary arterial pressure by fentanyl is caused by a decrease in pulmonary blood flow resulting from a decrease in cardiac output and mean arterial pressure.

In mice, fentanyl induced an increase in spontaneous motor activity, Straub tail reaction, increased muscle tone, respiratory depression and convulsions.

In dogs, fentanyl induced decreased motor activity, ataxia, decreased responsiveness to auditory and painful stimuli, respiratory depression, salivation and defecation. Nalorphine, 1 mg/kg IV caused an immediate reversal of the central depression induced by fentanyl, indicating that the compound was acting by an opioid-like mechanism.

Fentanyl induced a constipating effect in mice. In approximately equivalent analgesic doses, morphine appeared to have a greater constipating effect.

Fentanyl possesses a spasmogenic effect on the sphincter of Oddi in guinea pigs.

Human Pharmacology

The pharmacokinetics of fentanyl transdermal system were determined in serum of human surgical patients using radioimmunoassay and GC mass spectrophotometry. The time course of serum fentanyl concentrations was demonstrated during application and after removal of fentanyl transdermal system applied for 24 hours, daily application for 3 days, and system application for a 72-hour period.

Following initial system application, there is a 1 to 2 hour lag time before serum fentanyl concentrations are detected (0.2 mg/mL). Serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours. The amount of drug delivered by transdermal system fentanyl is proportional to the size of the system. Absorption of fentanyl continues throughout the entire 72-hour dosing interval. The serum fentanyl kinetics are linear within the dose range studied (25 - 100 mcg/h) and do not change with multiple doses.

Following system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20 hours. Following a 72-hour application, the mean half-life ranges from 20-27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life is 7 hours. Fentanyl delivered transdermally is 92% bioavailable.

As with other opioid analgesics, fentanyl produces respiratory depression which may last longer than the analgesic effect. The absolute duration cannot be stated definitively, because it will vary considerably depending on a number of factors, such as size and number of doses, method of administration, physical condition of the patient, other drugs given, if any, and the parameters of respiratory function that are observed. It has been reported, however, that in comparison with meperidine or morphine at doses producing similar degrees of respiratory depression, the onset and peak effect occur sooner with fentanyl and the observed parameters return to, or toward, control levels more rapidly.

The ventilatory effects of fentanyl, within the therapeutic range of 0.75 ng/mL to 3.0 ng/mL, were evaluated in normal volunteers. End tidal CO_2 concentration increased and the slope of the ventilatory-CO_2 response curve decreased with increasing fentanyl concentration. At equianalgesic serum concentrations, there were no significant differences between alfentanil, morphine and fentanyl on ventilatory effects.

Fentanyl can produce skeletal muscle rigidity, the occurrence of which is related primarily to the speed of intravenous injection.

Rarely, there have been reports of bronchoconstriction in conjunction with the use of IV fentanyl. It has been said that this effect is usually encountered in patients with allergic diathesis, such as bronchial asthma, and may be attributed to histamine release.

In general, fentanyl appears to produce only minimal effects on the cardiovascular system. There is a tendency toward transient bradycardia. There may be some hypotension, particularly following the administration of nitrous oxide to unstressed patients. However, in patients undergoing surgery, even when in relatively poor physical condition and given moderate to large doses, the relative stability of cardiovascular function has been particularly noted as well as the ability to reposition patients without significant blood pressure changes.

Observations on the occurrence of skin whealing at the injection site and assays of plasma histamine indicate that fentanyl rarely causes histamine release, and is therefore not likely to be associated with the opioid-induced hypotension attributed to this phenomenon.

Consistent with results seen in animal studies, fentanyl appears to be associated with minimal emetic activity in man. However, data from clinical studies can be difficult to interpret because they are subject to distortions introduced by such elements as the procedures being performed and the other drugs used.

TOXICOLOGY

Fentanyl has been administered by the oral, intravenous, intramuscular or subcutaneous routes either acutely or subacutely to rats, mice, guinea pigs, hamsters and cats. Laboratory animals tolerate relatively large doses of fentanyl in comparison to the doses recommended for human use (generally not more than 0.002-0.005 mg/kg).

Acute Toxicity

Intravenous LD_{50} determinations showed that the rat and guinea pig, with an LD_{50} in the 2 - 3 mg/kg range, were the most sensitive species tested; the mouse and dog were more tolerant, having LD_{50}'s in the 11 - 14 mg/kg range. Intramuscular LD_{50} determinations showed that the rat was the most sensitive species tested, having an LD_{50} of 1 mg/kg; the most tolerant species was the hamster with an LD_{50} of 65 mg/kg.

Carcinogenicity

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females (0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/h patch based on $AUC_{0\text{-}24h}$ comparison).

Subacute Toxicity - Rats

Four weeks of repeated administration of fentanyl by the intramuscular route (0, 0.1 and 0.4 mg/kg/day) and intravenous routes (0, 0.01, 0.02, 0.03, 0.05 and 0.075 mg/kg/day) were without effect on hematologic profile, food consumption, or gross or microscopic examination, with the exception of some local irritation at intramuscular sites. Intramuscular administration was associated with a low mortality incidence; following intravenous administration, mortality was present at 0.03 mg/kg/day and above.

Oral administration of fentanyl at doses of 5, 10, 20, 40, 80, 160 and 320 mg/kg/day for 14 days resulted in mortality at 10 mg/kg/day and above; survivors were noted to have bloody urine and bloody diarrhea which subsided during the second week of treatment.

Subacute Toxicity - Dogs

Intramuscular administration of 0, 0.1 and 0.4 mg/kg/day of fentanyl for four weeks did not produce significant effects on hematologic profile, body weight, organ weight, or gross or microscopic examinations. Intravenous administration of 0.1, 0.3 and 1.0 mg/kg/day for four weeks did not produce any mortality or significant gross lesions.

Physical signs associated with intravenous treatment included slight decrease in body weight, sedation, hypercapnia and decreased food consumption at all dosage levels, and convulsions principally at the high-dosage level. In addition, dogs in the high-dosage group had some pathology of the liver (mild cholestasis and granular cytoplasm in hepatocytes) and kidney (granular casts in collecting tubules or vacuolation) that may have been drug related; however, none of the lesions were considered severe or irreversible.

Tissue Irritation Studies

Tissue irritation studies demonstrated that transdermal system fentanyl elicited mild skin irritation and had little or no sensitization potential.

Studies of rabbits receiving 28 and 90 days of transdermal fentanyl administration showed no differences among the 3 treatment groups (negative control, TT placebo and TT fentanyl) with regard to hematology, blood chemistries or histological evaluations of skin and systemic tissues.

Teratology

Adult rats of a Wistar substrain were used in studies to determine the possible teratological effects of fentanyl on dams and their offspring. Three successive generations received fentanyl subcutaneously during the first 21 days of pregnancy, in daily doses of 0.04, 0.08, 0.16 and 0.31 mg/rat. No congenital abnormalities were produced in the experimental groups, but there were dose-related decreases in dam survival, survival *in utero* and average litter size and weight. A slight delay in delivery time and an increased mortality of the newborn were also observed in rats receiving fentanyl.

Mutagenicity

Fentanyl tested negative in the Ames Assay, UDS assay and Mammalian Cell Transformation Assay. Fentanyl did not cause chromosomal aberrations *in vitro* in human lymphocytes or in Chinese hamster ovary cells in the presence or absence of an exogenous metabolic source.

In the L5178Y Mouse Lymphoma Assay, fentanyl was nongenotoxic without activation. With activation, fentanyl at concentrations of 37 mcg/mL and higher demonstrated mutation frequencies above control levels; these concentrations are approximately 2,000 times greater than plasma levels observed with a fentanyl transdermal system in clinical use.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[N]TEVA-FENTANYL

fentanyl transdermal system

Read this carefully before you start taking TEVA-FENTANYL and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TEVA-FENTANYL**.**

Serious Warnings and Precautions

- **Even if you take TEVA-FENTANYL as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to overdose and death.**
- **Life-threatening breathing problems can happen while taking TEVA-FENTANYL, especially if not taken as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **Never give anyone your TEVA-FENTANYL. They could die from taking it. Touching the medicated side of a patch can cause a fatal overdose to people who have not been prescribed this medication, especially children. Avoid accidental contact between the patch and other people, especially when holding or caring for children.**
- **If you took TEVA-FENTANYL while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life- threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking TEVA-FENTANYL with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is TEVA-FENTANYL used for?

TEVA-FENTANYL is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around-the-clock painkillers
- the doctor determines that other treatment options are not able to effectively treat your pain

TEVA-FENTANYL is NOT used ("as needed") to treat pain that you only have once in a while.

How does TEVA-FENTANYL work?

TEVA-FENTANYL is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What is TEVA-FENTANYL?

TEVA-FENTANYL is a thin, adhesive, rectangular patch that is placed on your skin. TEVA-FENTANYL delivers an opioid medicine called fentanyl continuously through the skin and into the bloodstream to control your pain around the clock.

What to expect from TEVA-FENTANYL

Because the medicine in TEVA-FENTANYL is gradually released from the patch and slowly absorbed through the skin, do not expect immediate pain relief after you apply your first patch. During this initial period, your doctor may ask you to take additional pain medication until you experience the full benefits of TEVA-FENTANYL.

While most patients obtain adequate pain relief with TEVA-FENTANYL, your pain may vary and occasionally break through. This is not unusual. If this occurs, your doctor may prescribe additional pain medication.

It is important to let your doctor know whether or not your pain is under control. If you frequently need additional short-acting pain medication, or if pain is waking you at night, you may need a change in your TEVA-FENTANYL dose. **If you continue to have pain, call your doctor.**

Always follow your doctor's instructions carefully and do not change or stop your TEVA-FENTANYL medication without first consulting with your doctor.

What are the ingredients in TEVA-FENTANYL?

Medicinal ingredients: fentanyl

Non-medicinal ingredients:

- Peelable release liner: Polyethyleneterepthalate (PET or PETP) foil
- Backing film: backing foil
- Self adhesive drug containing the matrix: Polybutyltitanate and DuroTak®

TEVA-FENTANYL comes in the following dosage forms:
TEVA-FENTANYL is a transdermal patch that comes in five strengths: 2.063 mg, 4.125 mg, 8.25 mg, 12.375 mg, and 16.5 mg fentanyl per patch, delivering 12.5, 25, 50, 75, and 100 mcg fentanyl per hour respectively for 72 hours.

Do not use TEVA-FENTANYL if:
- you are allergic to fentanyl or any of the other ingredients of TEVA-FENTANYL
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing or other lung problems
- you have bowel blockage or narrowing of the stomach or intestines
- you are going to have, or recently had, a planned surgery
- you have never taken a strong opioid medication
- you are also taking MAO inhibitors (certain medicines used for treatment of depression) or have taken them in the last 14 days before treatment with TEVA-FENTANYL
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you get sudden severe pain in your abdomen and the cause has not been diagnosed
- you are pregnant or plan to become pregnant or in labour
- you are breastfeeding
- you are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-FENTANYL. Talk about any health conditions or problems you may have, including if you:
- have any other medical conditions (such as diseases of the heart, lung, brain, liver and kidney)
- have a history of sleep apnea or if anyone notices you stop breathing from time to time while sleeping
- have severe kidney or liver disease
- have problems with your pancreas
- have a head injury or brain tumour
- or a family member have a history of illicit or prescription drug or alcohol abuse
- have chronic and severe constipation
- suffer from migraines

Other warnings you should know about:

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to TEVA-FENTANYL. TEVA-FENTANYL can cause:
- drowsiness

- dizziness
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off TEVA-FENTANYL.

Serotonin Syndrome: TEVA-FENTANYL can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take TEVA-FENTANYL with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Fever/exposure to heat sources:
At high temperatures, greater than usual quantities of fentanyl can be released into your body. If you have a fever, you should contact your doctor, who may adjust your dose if necessary. Increased release of fentanyl can also result from direct exposure to heat sources.

Do not expose the patch area to **sources of heat** such as heating pads, electric blankets, heated waterbeds, heat lamps, saunas and hot tubs, intensive sunbathing, etc., as this may increase the drug's ability to go through the skin and therefore result in an overdose. This may also occur if you develop a fever.

Tolerance
TEVA-FENTANYL may lead to tolerance in the long run. It is therefore possible that your doctor will prescribe a higher dose of TEVA-FENTANYL after some time to

produce the same result.

Dependence
There is a possibility that you may become dependent on TEVA-FENTANYL (fentanyl) with longer term use. Discuss with your doctor.

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-FENTANYL:
- alcohol, including prescription and non-prescription medications containing alcohol. Do not drink alcohol while taking TEVA-FENTANYL. This can lead to drowsiness, depressed breathing, unusually slow or weak breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by TEVA-FENTANYL
- other opioid analgesics (for pain)
- general anaesthetics (used during surgery)
- benzodiazepines (drugs used to help you sleep or to reduce anxiety)
- antidepressants (for depression and mood disorders) such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs). Do not take TEVA-FENTANYL with MAO inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with TEVA-FENTANYL
- drugs used to treat migraines (e.g. triptans)
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- certain drugs used to treat convulsions (such as carbamazepine, phenobarbital or phenytoin)
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- anti-retroviral, anti-fungal and antibiotic drugs
- St. John's Wort

Patients should not consume grapefruit juice while taking this medication as it may make the side effects worse.

How to use TEVA-FENTANYL:

TEVA-FENTANYL should only be used on the skin.
- Make a note of the day, date and time the patch is applied, as a reminder of when it needs to be changed
- There is enough medicine on each patch to last 3 days (72 hours).
- Change the patch at the same time of day every 3 days (72 hours)
- Always remove the old patch before applying a new one. This is important to avoid overdose.

- If more than one patch is used, change all the patches at the same time
- Apply on clean, dry, intact, non-hairy area on your upper chest, upper back, or upper arm. If the area you choose has body hair, clip (do not shave) the hair close to the skin with scissors.
- If you need to clean the skin where the patch will be applied, use only clear water.

Do not:

- apply heat to the area before or after applying the patch.
- apply the patch on the same place twice in a row
- chew, swallow, put it in your mouth, or use the patch in any way other than on the skin.
- wear more than one patch at a time, unless your doctor tells you to.
- use the TEVA-FENTANYL patch if the seal is broken or the patch is cut, damaged or changed in any way.
- apply your patch in front of children since they may copy your actions
- exceed the dose recommended by your doctor.

Usual Adult Starting Dose

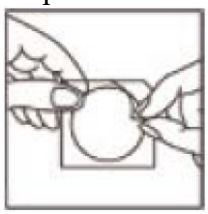
You should already be taking some type of strong opioid medication before you begin using TEVA-FENTANYL patches.

Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly.

Your doctor will determine the strength of TEVA-FENTANYL you should use based on your own particular needs. Do not change your dose without consulting your doctor. Each patch can be used for up to 72 hours (3 days). Taking higher doses can lead to more side effects and a greater chance of overdose.

How to apply TEVA-FENTANYL

Step 1.



Each patch is sealed in its own protective pouch. Do not remove the patch from the pouch until you are ready to use it. When you are ready, tear open the pouch at the notched corner.

Step 2.

A stiff protective liner covers the sticky side of the patch — the side that will be put on your skin. Hold the liner at the edge and pull the patch from the liner. Try not to touch the sticky side of the patch. Throw away the liner.

Step 3.

Immediately after you have removed the liner, apply the sticky side of the patch to a dry area of your chest, back, flank or upper arm. Press the patch firmly on your skin with the palm of your hand for about 30 seconds.

Not all adhesive products stick to all patients. If the patch does not stick well, or loosens after application, tape only the edges down with first aid tape.

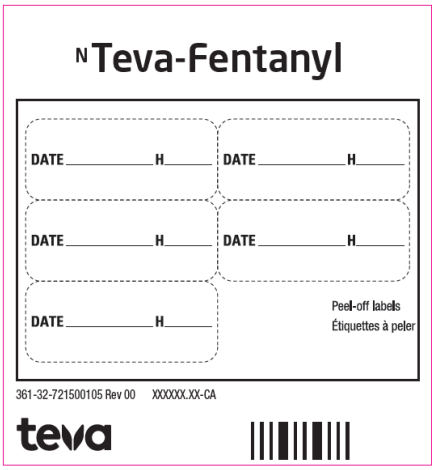
In the event that the patch falls off before 3 days or 72 hours, discard it (see **Disposal**) and apply a patch of the same strength at a different skin site. This may result in increased serum concentrations, therefore monitor the patient closely. Be sure to let your doctor know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your doctor).

Step 4. Wash your hands, with water only, when you have finished applying the patch.

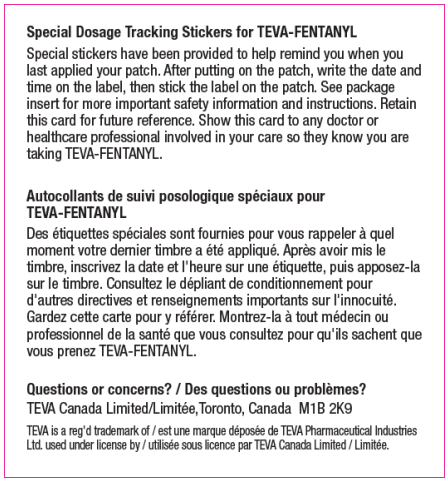
Step 5. Special labels are provided to help you remember when you last put on your patch. After putting on the patch, write the date and time on a label, then stick the label on the patch. Retain the card for future reference. Show the card to any doctor or healthcare professional involved in your care so they know you are taking TEVA-FENTANYL.

An example of the sample special tracking sticker is illustrated below:

Front Panel:



Back Panel:



Special Dosage Tracking Stickers for TEVA-FENTANYL

Special stickers have been provided to help remind you when you last applied your patch. After putting on the patch, write the date and time on the label, then stick the label on the patch. See package insert for more important safety information and instructions. Retain this card for future reference. Show this card to any doctor or healthcare professional involved in your care so they know you are taking TEVA-FENTANYL.

Autocollants de suivi posologique spéciaux pour TEVA-FENTANYL

Des étiquettes spéciales sont fournies pour vous rappeler à quel moment votre dernier timbre a été appliqué. Après avoir mis le timbre, inscrivez la date et l'heure sur une étiquette, puis apposez-la sur le timbre. Consultez le dépliant de conditionnement pour d'autres directives et renseignements importants sur l'innocuité. Gardez cette carte pour y référer. Montrez-la à tout médecin ou professionnel de la santé que vous consultez pour qu'ils sachent que vous prenez TEVA-FENTANYL.

Questions or concerns? / Des questions ou problèmes?

TEVA Canada Limited/Limitée,Toronto, Canada M1B 2K9

TEVA is a reg'd trademark of / est une marque déposée de TEVA Pharmaceutical Industries Ltd. used under license by / utilisée sous licence par TEVA Canada Limited / Limitée.

Step 6. After wearing the patch for 3 days, or as directed by your doctor, remove it (see **Disposal**). Then choose a **different** place on your skin to apply a new patch and repeat steps 1 to 5 in order. **Do not apply the new patch to the same place as the last one until several days have lapsed.**

Water and TEVA-FENTANYL

You can bathe, swim, or shower while you are wearing TEVA-FENTANYL. If the patch falls off, discard the patch properly (see **Disposal**) and apply a new one at a different skin site, making sure the new skin area you choose is dry. Be sure to let your doctor know that this has happened. Take note of the time you applied the new patch and change it only after the required number of hours.

Missed Dose:

If a patch is left on for more than three days (72 hours), remove patch and apply a new patch following instructions given (see **How to use TEVA-FENTANYL**).

Discontinuation of TEVA-FENTANYL:

Please do not suddenly stop taking TEVA-FENTANYL as it may cause unwanted side effects such as nausea, vomiting, diarrhea, anxiety and shivering. Your doctor can discuss the best way for you to stop taking TEVA-FENTANYL.

Refilling Prescriptions for TEVA-FENTANYL:

A new written prescription is required from your doctor each time you need more TEVA-FENTANYL. Therefore, it is important that you contact your doctor before your current supply runs out.

What are possible side effects from using TEVA-FENTANYL?

These are not all the possible side effects you may feel when taking TEVA-FENTANYL. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness, insomnia
- Dizziness, fainting
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness, lack of coordination
- Itching, hives, or inflammations
- Skin irritations (thinning or redness; ulcer (sore) where the patch has been
- Sweating
- Constipation
- Confusion
- Seeing, feeling, hearing or smelling things that are not there (hallucinations)
- Depression
- Low level of oxygen in the blood
- Stopping breathing from time to time while sleeping

Be aware that removing the patch does not completely remove the source of drug, as drug is deposited under the skin and will continue to be released into the bloodstream over the next hours after the patch is removed.

Opioid Withdrawal Symptoms
Opioid withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety and shivering are possible after converting from your previous opioid analgesic to TEVA-FENTANYL, or converting from TEVA-FENTANYL to another opioid. Contact your doctor if you experience these symptoms when switching to or from TEVA-FENTANYL.

Talk with your doctor or pharmacist about ways to prevent constipation when you start using TEVA-FENTANYL.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion or extreme drowsiness.

If a person is having the above signs of overdose, check all areas of their skin and remove any patches. There may be more than one patch, if a previous patch was not removed. Wash the area with water and seek immediate emergency medical help.

If you think you, or a person you are caring for, have taken too much TEVA-FENTANYL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Serious side effects and what to do about them			
Symptom/ effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin			✓
Respiratory Depression: slow, shallow or weak breathing.			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea.			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		
Seizures (convulsions)			✓
Stevens-Johnson Syndrome: Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals.			✓
Serotonin syndrome: A combination of most or all of the following; agitation, tremor, confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat, labile blood pressure, nausea, vomiting, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health

Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep unused, used, or expired TEVA-FENTANYL in a secure place to prevent theft, misuse or accidental exposure. It may harm people who may take this medicine by accident, or intentionally when it has not been prescribed for them.

Keep TEVA-FENTANYL in its protective pouch until you are ready to use it. Store TEVA-FENTANYL between 15° and 25°C. Do not refrigerate or freeze. Remember, the inside of your car can reach temperatures much higher than 30°C on a sunny day. Do not carry pouch in your pocket as it may reach body temperature (36°C).

Keep TEVA-FENTANYL out of the sight and reach of children and pets.

Disposal:
Before putting on a new TEVA-FENTANYL patch, remove the patch you have been wearing. Fold the used patch in half so the sticky side sticks to itself. If the drug adhesive layer accidentally contacts the skin, the area should be washed with clear water. A used TEVA-FENTANYL can be very dangerous for, or even lead to death in babies, children, pets, and adults who have not been prescribed TEVA-FENTANYL as a considerable amount of drug remains in the patch after use.

TEVA-FENTANYL should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

Wash your hands, with water only, after removing the patch.

Dispose of any patches that are left over from your prescription as soon as they are no longer needed. Remove the left-over patches from their protective pouches and remove the protective liners. Fold the patches in half and return to a pharmacy for proper disposal.

Safety and handling:
TEVA-FENTANYL is sealed to keep the drug adhesive layer from getting on your hands or body. If the drug adhesive layer accidentally touches the skin, wash the area with large amounts of water. Do not use soap, alcohol, or other solvents as these may increase the drug's ability to go through the skin.

Serious medical consequences, including death, have occurred when patches were accidentally transferred to other people, for example while hugging, sharing a bed or moving a patient. If your patch dislodges and accidentally sticks to the skin of another person, take the patch off immediately, wash the area with water, and get medical care for them right away. This is true for both fresh and used patches, as a considerable amount of drug remains in the patch after use.

If you want more information about TEVA-FENTANYL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario, Canada M1B 2K9.

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