PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

®FENTANYL INJECTION BP

Fentanyl 50 mcg/mL as fentanyl citrate

Narcotic Analgesic
Adjunct to Anesthesia

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous Intramuscular Epidural	Solution / 50 mcg/mL	The solution may contain sodium hydroxide or citric acid for pH adjustment.

INDICATIONS AND CLINICAL USE

Adults
Fentanyl Injection BP, administered by intravenous or intramuscular injection, is indicated:

- For analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises;
- For use as narcotic analgesic supplements in general or regional anesthesia;
- For administration with a neuroleptic such as droperidol injection as an anesthetic premedication, for induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia; and
- For use as anesthetic agents with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

Fentanyl Injection BP, by epidural administration, is indicated for the post-operative management of pain following general surgical procedures and cesarean sections.

Fentanyl Injection BP is not indicated as an as-needed (prn) analgesic.

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.

Pediatrics (< 2 years of age)
The safety and efficacy of fentanyl has not been studied in children younger than 2 years of age. Therefore the use of Fentanyl Injection BP is not recommended in patients under 2 years of age.

CONTRAINDICATIONS

- 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.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Patients exhibiting septicemia.
- Patients exhibiting severe hemorrhage or shock.
- Patients exhibiting local infection at the site of proposed puncture.
- Patients exhibiting disturbance in blood morphology and/or anticoagulant therapy or other concomitant drug therapy or medical conditions which could contraindicate the technique of epidural 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 risks of overdose and death with immediate release opioid formulations, Fentanyl Injection BP should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

As with other CNS depressants, patients who have received fentanyl should have appropriate surveillance. Resuscitative equipment and a narcotic antagonist such as naloxone should be readily available to manage apnea.

Addiction, Abuse, and Misuse

Fentanyl Injection BP 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 Fentanyl Injection BP and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS, Abuse and Misuse). Fentanyl Injection BP 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 Fentanyl Injection BP. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Fentanyl Injection BP or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental exposure of even one dose of Fentanyl Injection BP, especially by children, can result in a fatal overdose of fentanyl (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

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

Interaction with Alcohol

The co-ingestion of alcohol with Fentanyl Injection BP should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS, General, and DRUG INTERACTIONS, Drug-Lifestyle Interactions).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (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 Fentanyl Injection BP 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

Fentanyl Injection BP should be stored securely to avoid theft or misuse.

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

If fentanyl is administered with a tranquilizer such as droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available (see **DRUG INTERACTIONS**).

Patients should be cautioned not to consume alcohol while taking Fentanyl Injection BP as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of fentanyl can occur at particularly high doses. A fentanyl dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, Fentanyl Injection BP is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Fentanyl Injection BP 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 Fentanyl Injection BP, 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.

Cardiovascular

Fentanyl administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Fentanyl Injection BP.

The use of Fentanyl Injection BP in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see **DOSAGE AND ADMINISTRATION**).

Vital signs should be monitored routinely. Fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Fentanyl Injection BP and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, 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, goosebumps, 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 **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).**

Use in Drug and Alcohol Addiction

Fentanyl Injection BP is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Fentanyl Injection BP; extreme caution and awareness is warranted to mitigate the risk.

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.

Gastrointestinal Effects

Fentanyl and other morphine-like opioids have been shown to decrease bowel motility. Fentanyl may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

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.

Fentanyl Injection BP is not recommended to be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the risks. If Fentanyl Injection BP was used during pregnancy, special attention to NOWS is warranted.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): 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. Respiratory depression, hypotension and profound sedation, coma or death may result.

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 Fentanyl Injection BP 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**). Fentanyl Injection BP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation;** 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 Injury: The respiratory depressant effects of fentanyl, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, fentanyl may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, fentanyl must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

Serotonin Syndrome: Fentanyl Injection BP could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued 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) occur and supportive symptomatic treatment should be initiated. Fentanyl Injection BP 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**).

Patient Counselling Information

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 Fentanyl Injection BP. Women who are breast-feeding or pregnant should be informed of the risks to their baby if they are exposed to Fentanyl Injection BP in utero or through breast milk.

Peri-Operative Considerations

Fentanyl Injection BP are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Fentanyl Injection BP for at least 24 hours before the operation and Fentanyl Injection BP should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if 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. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Fentanyl and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Fentanyl Injection BP should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Fentanyl Injection BP may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of fentanyl with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Respiratory

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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Fentanyl should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Fentanyl Injection BP, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Fentanyl Injection BP and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Injection BP is essential. Overestimating the Fentanyl Injection BP dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, Special Populations, **Special Risk Groups**; and **DOSAGE AND ADMINISTRATION**).

As with other potent narcotics, the respiratory depressant effect of fentanyl may persist longer than the measured analgesic effects. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially as low as one-fourth to one-third those usually recommended.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. In addition, skeletal muscle movements of various groups in the extremities, neck and external eye have been reported during induction of anesthesia with fentanyl; these reported movements have, on rare occasions, been strong enough to pose patient management problems. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

WHERE MODERATE OR HIGH DOSES ARE USED (ABOVE 10 mcg/kg), THERE MUST BE ADEQUATE FACILITIES FOR POSTOPERATIVE OBSERVATION AND VENTILATION, IF NECESSARY, OF PATIENTS WHO HAVE RECEIVED FENTANYL. IT IS ESSENTIAL THAT THESE FACILITIES BE FULLY EQUIPPED TO HANDLE ALL DEGREES OF RESPIRATORY DEPRESSION.

Fentanyl may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia and bronchoconstriction.

Conduction Anesthesia: Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics can alter respiration by blocking intercostal nerves. Through other mechanisms, fentanyl can also alter respiration (see ACTION AND CLINICAL PHARMACOLOGY). Therefore, when fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological actions involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Fentanyl Injection BP, as in these patients, even usual therapeutic doses of Fentanyl Injection BP may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Fentanyl Injection BP is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

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-Marketing Experience**).

Special Populations

Special Risk Groups: Fentanyl should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in humans have not been conducted. Fentanyl Injection BP crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, can be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Fentanyl Injection BP is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can 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 Fentanyl Injection BP is used in this population.

Pediatrics (< 2 years of age): The safety and efficacy of fentanyl has not been studied in pediatric populations under 2 years of age. Therefore, the use of Fentanyl Injection BP is not recommended.

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 and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic or Renal Impairment: Fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of Fentanyl Injection BP are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently observed serious adverse effects of fentanyl are respiratory depression, apnea, muscle rigidity and bradycardia. If these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Pruritus, occurring mainly in the face and chest area, is observed frequently following the administration of fentanyl by the epidural route. Other adverse reactions that have been reported are: cough, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, itching, drowsiness and urinary retention.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.
When a neuroleptic such as droperidol is used with fentanyl, the following adverse reactions can occur: chills or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of droperidol.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of fentanyl combined with droperidol. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

Although fentanyl has been reported to induce grand mal seizures with intravenous administration at doses of 100 mcg, there was no electroencephalographic documentation. Some authors suggest that rigidity is a more likely explanation for the myoclonic movements, since none of the patients showed any neurologic disorders after their reported seizures.

Clinical Trial Adverse Drug Reactions

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If

it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Post-Marketing Experience

Serotonin Syndrome: 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 or a Serotonin Norepinephrine Re-uptake Inhibitor (see **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

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for

whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). Fentanyl Injection BP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions
When a neuroleptic such as droperidol is used with fentanyl, pulmonary arterial pressure may decrease. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

When either high doses or anesthetic doses of fentanyl are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics and general anesthetics) will have additive or potentiating effects with fentanyl. When patients have received such drugs, the dose of fentanyl required will be less than usual. Likewise, following the administration of fentanyl, the dose of other CNS depressant drugs should be reduced.

When fentanyl is used with a neuroleptic, such as droperidol, hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents **other than epinephrine** should be considered. Because of the alpha-adrenergic blocking action of droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with droperidol.

When droperidol is used with fentanyl and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. The use of fentanyl in patients who are taking or have received MAO inhibitors within 14 days is contraindicated (see **CONTRAINDICATIONS**).

Serotonergic Drugs: Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

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

DOSAGE AND ADMINISTRATION

Fentanyl Injection BP should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non- opioid analgesics).

Fentanyl Injection BP is administered by intravenous, intramuscular, or epidural injection.

Dosage should be individualized. Some of the factors to be considered in determining the dose are: age, body weight, physical status, underlying pathological condition, use of other drugs and the surgical procedure involved. Vital signs should be monitored routinely.

For acute pain, it is recommended that Fentanyl Injection BP be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 0.9 mg (90 morphine milligram equivalent) of Fentanyl Injection BP not be exceeded. Each patient should be assessed for their risk prior to prescribing Fentanyl Injection BP, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Fentanyl Injection BP (see DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Dosing Considerations

Fentanyl Injection BP should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

Recommended Dose and Dosage Adjustment

Adults:

Premedication:

As premedication (to be appropriately modified in the elderly, debilitated and those who have received other depressant drugs), 0.7 to 1.4 mcg/kg (0.014 to 0.028 mL/kg) may be administered intramuscularly 30 to 60 minutes prior to surgery.

Adjunct to General Anesthesia:

See **Dosage Range Chart (Table 1).**

Adjunct to Regional Anesthesia:

With regional anesthesia, 0.7 to 1.4 mcg/kg (0.014 to 0.028 mL/kg) may be administered

intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

As a General Anesthetic:
When attenuation of responses to surgical stress is especially important, fentanyl in doses of 50 to 100 mcg/kg (1 to 2 mL/kg) may be administered with oxygen and a muscle relaxant to produce anesthesia without the use of additional anesthetic agents.

In certain cases, doses up to 150 mcg/kg (3 mL/kg) may be necessary to produce the anesthetic effects.

Table 1. Dosage Range Chart (Adjunct to General Anesthesia)

Low Dose	Moderate Dose	High Dose
(Minor Surgical Procedures) **2 mcg/kg (0.002 mg/kg; 0.04 mL/kg) Fentanyl Injection BP.** Fentanyl in small doses is useful for minor but painful surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period.	(Major Surgical Procedure) **2-20 mcg/kg (0.002 mg/kg-0.02 mg/kg; 0.04-0.4 mL/kg) Fentanyl Injection BP.** Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential.	(Open Heart and Certain Complicated Procedures Involving Prolonged Surgery) **20-50 mcg/kg (0.02-0.05 mg/kg; 0.4 mL - 1 mL/kg) Fentanyl Injection BP.** During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20 to 50 mcg/kg (0.02 - 0.05 mg/kg; 0.4 - 1 mL/kg) of Fentanyl Injection BP with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin. When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression. The main objective of this technique would be to produce "stress free" anesthesia.
Additional doses are infrequently needed in these minor procedures.	**MAINTENANCE DOSAGE** **10-25 mcg (0.01-0.025 mg; 0.2-0.5 mL) Fentanyl Injection BP** administered intravenously or intramuscularly when movement or changes in vital signs indicate surgical stress or lightening of analgesia.	**Maintenance dosage (ranging from 25 mcg (0.025 mg; 0.5 mL) to one half the initial loading dose) Fentanyl Injection BP** will be dictated by changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

Fentanyl has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is indicated, and for

certain complicated neurological and orthopedic procedures**.**

Post-Operative Pain
For the post-operative management of pain following general surgical procedures and cesarean sections, fentanyl may be administered by the epidural route at a dose of 100 mcg (0.1 mg, 2 mL). The 2 mL fentanyl should be diluted with 8 mL of 0.9% sodium chloride resulting in a final concentration of 10 mcg/mL. If required, additional boluses of 100 mcg on demand or by continuous infusion at rate of 1 mcg/kg/hr. Caution: Such admixtures should be used within 24 hours because of the risk of microbial contamination during preparation.

It is essential that qualified personnel and adequate facilities are available for the management of respiratory distress.

Refer to **Table 2** for the approximate opioid analgesic equivalences.

Opioid Rotation:
Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50 % to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 2: Opioid Analgesics: Approximate Analgesic Equivalences[1]

Drug	Equivalent Dose (mg)[2] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	**Oral**	
Strong Opioid Agonists:			
Morphine	10	60[3]	3-4
Oxycodone	15	30[4]	2-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Meperidine[6]	75	300	1-3
Oxymorphone	1.5	5 (rectal)	3-4
Methadone[5]	-	-	-
Heroin	5-8	10-15	3-4
Weak Opioid Agonists:			
Codeine	120	200	3-4
Propoxyphene	50	100	2-4
Mixed Agonist-Antagonists[7]:			
Pentazocine[6]	60	180	3-4
Nalbuphine	10	-	3-6
Butorphanol	2	-	3-4

Footnotes:
[1]References:

- Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42- 2/5-1984E.
- Foley KM. The treatment of cancer pain. *New Engl. J. Med.* 1985;313(2):84-95.

- Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM. editor. Evaluation and treatment of chronic pain, 2nd Ed. Baltimore(MD): Williams and Wilkins; 1992. p. 359-68.
- Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd Ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.[†] Upward titration may be required to reach appropriate maintenance doses.

[†]Levy MH. Pharmacologic treatment of cancer pain. *N Engl J Med* 1996;335:1124-1132.

[3] For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).

[4] Based on single entity oral oxycodone in acute pain.

[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[6] Not recommended for the management of chronic pain.

[7] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Geriatrics:
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Fentanyl Injection BP should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatric (≥ 2 years of age):
For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 2 to 3 mcg/kg (0.04 to 0.06 mL/kg) of body weight is recommended.

Use with Non-Opioid Medications:
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Fentanyl Injection BP can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Fentanyl Injection BP. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, goosebumps, 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.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. 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 individualised 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.

Opioid analgesics may only be 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 advanced cancer suffering from some of these forms 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.

Disposal

Fentanyl Injection BP should be kept in a safe place, out of the sight and reach of children before, during and after use. Fentanyl Injection BP should not be used in front of children, since they may copy these actions.

Fentanyl Injection BP should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired Fentanyl Injection BP should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. 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.

Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms: The manifestations of fentanyl overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours, body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

It is not known whether fentanyl is dialyzable.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fentanyl, although chemically unrelated to morphine, produces pharmacologic effects and degree of analgesia similar to morphine. On a weight basis, however, fentanyl is 50 to 100 times more potent than morphine, but its duration of action is shorter than that of meperidine or morphine. A parenteral dose of 100 mcg (2.0 mL) of fentanyl is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine.

The principal actions of therapeutic value are analgesia and sedation (see **DETAILED PHARMACOLOGY**).

Pharmacodynamics

Fentanyl has been reported to be a narcotic analgesic with a rapid onset and a short duration of action.

Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics may last longer than the analgesic effect. As the dose of the narcotic is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that clinically significant histamine release rarely occurs with fentanyl. Assays in man demonstrate no clinically significant histamine release in dosages up

to 50 mcg/kg (0.05 mg/kg; 1 mL/kg). Fentanyl preserves cardiac stability and at higher doses, inhibits stress-related hormonal changes.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of narcotic analgesics including euphoria, miosis, bradycardia and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effects may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100 mcg (0.1 mg; 2.0 mL).

Following intramuscular administration, onset of action is from 7 to 8 minutes, and the duration of action is one to two hours.

Following epidural administration, onset of analgesia occurs between 5 and 10 minutes and the duration of action is generally 2 to 5 hours. Analgesia can be maintained with on-demand or continuous epidural administration.

As with longer acting narcotic analgesics, the duration of respiratory depressant effect may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO_2 stimulation following administration of fentanyl to man:

(i) Diminished sensitivity to CO_2 stimulation may persist longer than depression of respiratory rate. Altered sensitivity to CO_2 stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 mcg (0.6 mg; 12 mL) of fentanyl to healthy volunteers. Fentanyl frequently slows the respiratory rate, duration and degree of respiratory depression being dose related.

(ii) The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection (see **WARNINGS AND PRECAUTIONS**).

Fentanyl, in commonly used clinical doses (less than 10 mcg/kg) has little or no effect on myocardial or hemodynamic function except for vagally induced bradycardia.

The effects of low doses of fentanyl (0.07 mcg/mL and 0.36 mcg/mL) on hemoglobin affinity for oxygen have been studied in comparison to other analgesics. It has been reported that such doses shifted the hemoglobin dissociation curve to the left, but a higher dose (0.71 mcg/mL) failed to alter this curve.

In patients scheduled for coronary artery bypass, fentanyl at doses of 37 mcg/kg followed by 53 mcg/kg intravenously, showed instances of hemolysis; however the clinical significance is still to be defined.

The circulatory effects of fentanyl at 5 sequential intravenous doses of 1 mcg/kg intravenous were studied in conscious and anesthetized subjects. In conscious patients, fentanyl did not affect the pressure or heart rate, while in anesthetized patients, a 20% fall in blood pressure and heart rate was noted.

Fentanyl has been used in fourteen neonates undergoing major surgical procedures; doses of 10 mcg/kg, 25 mcg/kg or 50 mcg/kg were given intravenously. An extremely prolonged ventilatory depression, 1.5 to 2 times the normal adult value and transient rebounds in plasma levels were noted.

Central Nervous System:
Fentanyl produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Fentanyl causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of fentanyl overdose.

Gastrointestinal Tract and Other Smooth Muscle:
Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:
Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

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

Immune System:
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics

With intravenous doses of approximately 3 to 30 mcg/kg in humans, the serum curves could be described in terms of a three-compartment open model.

At all doses, plasma levels have been reported to fall rapidly in the first 5 minutes to approximately 20% of the peak value.

The elimination half-life is approximately:
- from 0.73 to 1.63 minutes for the first distribution phase,
- from 5.1 to 21 minutes for the second phase,
- from 86.6 to 346.5 minutes for the third phase.

Urinary excretion was very low during the first two hours.

Metabolism and Excretion:
The concentration of fentanyl excreted unchanged in the urine is usually about 8 to 10%. The liver is the most important metabolizing organ, whereas extrahepatic metabolism occurs only to a very minor degree in the kidney.

The metabolites of fentanyl are reported to be: phenylacetic acid, norfentanyl (4-N-(N-propionyl-3H-anilino)piperidine), propionic acid and despropiofentanyl (1-2 (phenethyl)-4-N-anilinopiperidine).

Special Populations and Conditions

Pediatrics: Individuals under 2 years of age should not take Fentanyl Injection BP.

Geriatrics: 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.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light. Protect from freezing. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

Fentanyl Injection BP may be diluted with Sodium Chloride Injection USP 0.9%. Admixtures should be used within 24 hours.

As with all parenteral products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

Pharmacy Bulk Vial
The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized parenteral admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for

the preparation of admixtures only. Dispensing from a Pharmacy Bulk Vial should be completed as soon as possible after initial entry.

Fentanyl citrate is reported to be physically incompatible with methohexital sodium, pentobarbital sodium, and thiopental sodium.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Fentanyl Injection BP is a preservative free, sterile aqueous solution. Each mL of solution contains: fentanyl 50 mcg (as citrate), citric acid and/or sodium hydroxide to adjust pH and water for injection.

Fentanyl Injection BP is supplied in 2 mL ampoules, boxes of 10.

Fentanyl Injection BP is also supplied in the following:

- 5 mL single use glass vials, boxes of 10,
- 20 mL single use glass vials, boxes of 5,
- 50 mL Pharmacy Bulk Vials, boxes of 1.

LATEX-FREE STOPPER - Stopper contains no dry natural rubber.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

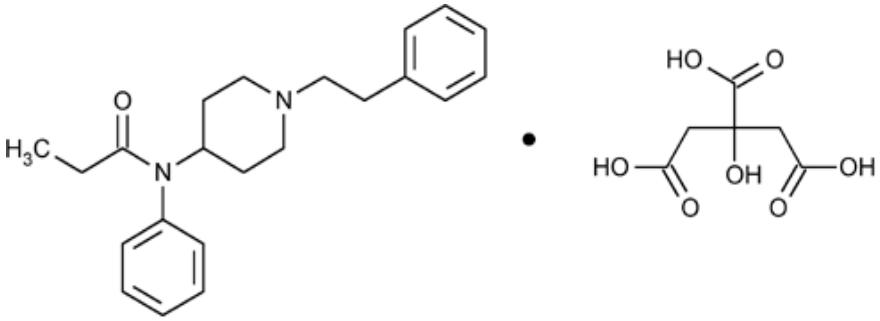
Drug Substance

Chemical Group: Fentanyl citrate is an anilinopiperidine-derivative opioid analgesic.

Proper Name: Fentanyl citrate.

Chemical Name: Propanamide, *N*-phenyl-*N*- [1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

Structural Formula:



Molecular Formula: $C_{22}H_{28}N_20 \bullet C_6H_80_7$

Molecular mass: 528.60 g/mol

Free Base Molecular mass: 336.5

Description: Fentanyl citrate is a white to pale yellow crystalline powder. Itis partially soluble in water, soluble in methanol, and slightly soluble in ethanol, chloroform and in ether.

DETAILED PHARMACOLOGY

Animal Pharmacology

Mice
Fentanyl was effective in a modified Haffner tail clamp test in mice, to detect analgesic activity. The ED_{50} for fentanyl was reported to be 0.8 mg/kg subcutaneously and that for morphine, 15 mg/kg subcutaneously. The onset of the analgesic effect occurred in 4 minutes with fentanyl and the duration was 30 minutes.

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

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

Rats
Fentanyl 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 morphine.

At high doses (25 to 400 mcg/kg) fentanyl has been reported to affect cerebral circulation and metabolism in rats. Seizures are noted in about 25% of rats receiving either 200 mcg or 400 mcg/kg.

Rabbits
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.

Cats
Fentanyl, like other potent narcotic analgesic, produces skeletal muscle rigidity. This muscular rigidity can be blocked or reversed by succinylcholine.

Fentanyl in doses of 10, 20, 40, 80 and 160 mcg/kg has been demonstrated to have no effect on neuromuscular transmission in anesthetized cats.

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

Dogs
In dogs, fentanyl induced decreased motor activity, ataxia, decreased responsiveness to auditory and painful stimuli, respiratory depression, salivation and defecation. Nalorphine 1 mg/kg, injected

intravenously, caused an immediate reversal of the central depression induced by fentanyl, indicating that the compound was acting by a narcotic-like mechanism.

Fentanyl was administered to anesthetized dogs in increasing intravenous dosages from 2.5 mcg to 160 mcg/kg. These doses caused no change in left ventricular pressure. Doses up to 30 mcg/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.
Other studies conducted in anesthetized dogs demonstrate that fentanyl injected intravenously at 25 mcg/kg 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.

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

When fentanyl was administered to anesthetized dogs with experimental coronary occlusion at a intravenous dose of 50 mcg/kg, 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 10 and 50 mcg caused no change in femoral blood flow. Intra-arterial injection of 200 mcg 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.

After coronary artery occlusion, fentanyl at a dose of 100 mcg/kg did not affect either regional myocardial blood flow or myocardial infarct size in dogs.

At doses of 50 mcg/kg in anesthetized dogs, fentanyl has been reported to produce a constriction of the renal vascular bed.

The interaction of fentanyl with diazepam and pancuronium was investigated in the anesthetized dogs. Fentanyl alone in an intravenous dose of 500 mcg/kg decreased heart rate, cardiac output and arterial pressure. The intravenous administration of diazepam 0.5 mg/kg 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.

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

TOXICOLOGY

Fentanyl had been studied by the oral, intravenous, intramuscular or subcutaneous routes, in mice, dogs, rats and cats.

Laboratory animals tolerate relatively large doses of fentanyl in comparison to the dose recommended for human use.

Acute Toxicity

Table 3. Acute Toxicity of Fentanyl

Species	Route	LD_{50} (mg/kg)
Mice	intravenous	11.2 (7.4 - 16.8)
	subcutaneous	62.0 (27.0 - 142.0)
Rats	intravenous	6.0 (4.6 - 7.7)
	subcutaneous	12.0 (7.9 - 19.6)
	oral	18.0 (9.4 - 32.4)

Mice
Following subcutaneous administration of fentanyl citrate at doses ranging from 1 to 300 mg/kg in mice, the following effects were noted: increase in spontaneous motor activity, circling, increased response to touch, Straub tail reaction, mydriasis, increased muscle tone, respiratory depression, convulsions, followed by death.

The onset of these effects was seen with doses of fentanyl citrate of 1 mg/kg within 1-2 minutes after injection. The duration of behavioral changes with a dose of 1 mg/kg was approximately one hour, and from four to six hours with high doses.

In the lethal dose range, blanching of the cornea and initial depression followed by stimulation were reported. Some deaths were also observed at doses of 3-4 mg/kg of fentanyl citrate, which are approximately one-fifteenth the calculated LD_{50}. A biphasic mortality dose-response curve was also observed following intravenous administration.

Rats
Doses of 25 to 400 mcg/kg fentanyl citrate were given as an intravenous bolus to rats. Twenty-five percent of animals receiving the highest dosage exhibited changes compatible with seizure activity. These seizures may be abolished by naloxone.

Dogs
Repeated intravenous administration of fentanyl citrate at doses of 10, 20, 40 mcg/kg, spaced 15-30

minutes apart, showed a reduction in respiratory minute volume. Maximum depression was seen within one minute after administration and recovery occurred within 5 minutes.

Intramuscular administration of fentanyl citrate at doses of 12.5, 25, 50, 100, 200 and 1000 mcg/kg produced similar effects at all dose levels, namely decreased motor activity, ataxia, bradycardia, respiratory depression, salivation and defecation. No mortality was reported.

From the studies reported on these species, the rat seems to be very sensitive to fentanyl, while dogs and mice are more tolerant.

Tolerance Studies

Rats
Rats given fentanyl, 40 mcg/kg every second day for a total of 10 days, developed tolerance within two days. The degree of tolerance increased until at least the tenth day, and persisted for at least 24 days after the initial administration.

In a series of experiments in rats, conducted over a period of 15 weeks, with intravenous doses of fentanyl ranging from 2.5 to 20 mcg/kg, it has been found that the discriminative stimulus properties of fentanyl are not subject to any detectable tolerance.

Dogs
The effect of fentanyl on electric stimulation-induced cardiovascular changes has been studied in anesthetized dogs. In untreated dogs, electric stimulation of a branch of the radial nerve elicits an increase in heart rate (HR) and mean arterial pressure (AP). Fentanyl, 100 mcg/kg, injected intravenously, decreased the HR and AP responses by 85 and 70%, respectively, 5 min after injection. The evoked cardiovascular responses returned to pretreatment levels 90 min after drug administration. In a second group of dogs, fentanyl, 100 mcg/kg, injected intravenously, was administered subsequent to bolus, graded doses (ranging from 1.5 to 63 mcg/kg), administered at 20 min intervals. The graded doses of fentanyl induced acute tolerance, so that 5 min after the injection of the 100 mcg/kg intravenous dose, the drug had little effect upon the stimulation induced cardiovascular changes, namely, the increase in AP was not affected and the increase in HR was only slightly attenuated. Ninety minutes after the injection of the 100 mcg/kg dose of fentanyl, both the HR and AP responses were enhanced indicating a rebound phenomenon. The study indicates that conditioning an animal for three hours with fentanyl induces tolerance to the depressant effect of the drug upon evoked cardiovascular reflexes.

Cumulative effects
Multiple administration of fentanyl at doses of 40 mcg/kg in rats lead to cumulative analgesic effects (rat tail flick method) after the fourth administration.

Reproduction and teratology
Fentanyl was administered continuously to Sprague-Dawley rats, using chronically implanted osmotic minipumps. The drug was given at doses of 10, 100 and 500 mcg/kg/day for two weeks prior to breeding and throughout pregnancy until day 21, when the dams were sacrified. At the

highest dose, 4/28 rats died within 24 hours after implantation of the pump.

No other drug-related adverse effects have been reported. Rats gained similar amounts of weight during pregnancy and blood gas values were normal. Fentanyl has been found to be devoid of adverse reproductive and teratogenic effects.

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Preclinical

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

®FENTANYL INJECTION BP
Fentanyl 50 mcg/mL as fentanyl citrate

Read this carefully before you start taking Fentanyl Injection BP. This leaflet is a summary and will not tell you everything about these drugs. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Fentanyl Injection BP.

Serious Warnings and Precautions

- **Even if you take Fentanyl Injection BP as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Fentanyl Injection BP. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your Fentanyl Injection BP. They could die from taking it. If a person has not been prescribed Fentanyl Injection BP, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Fentanyl Injection BP 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

- **Fentanyl Injection BP should only be administered by persons with the appropriate training and experience with these kind of drugs.**

- **Complete resuscitation (life-saving) equipment and an antidote to rapidly counteract the effects of the drug should always be available.**

- **Taking Fentanyl Injection BP 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 Fentanyl Injection BP used for?

Fentanyl Injection BP is indicated for the following uses:

When injected in a vein
- For pain relief of short duration during prior to, during and immediately after general or regional anesthesia.

When injected in the spine
- For pain relief after surgery, and during labour and vaginal delivery.

How does Fentanyl Injection BP work?

Fentanyl Injection BP is a painkiller belonging to the class of drugs known as opioids. They relieve pain by acting on specific nerve cells of the spinal cord and brain.

Fentanyl Injection BP will provide pain relief when injected in a vein prior to, during and immediately after general or regional anesthesia. When injected in the spine after surgery, during labour and vaginal delivery, it provides pain relief.

What are the ingredients in Fentanyl Injection BP?

Each mL of Fentanyl Injection BP solution contains: fentanyl 50 mcg (as citrate), citric acid and/or sodium hydroxide to adjust pH and water for injection.

Fentanyl Injection BP comes in the following dosage forms:

Fentanyl Injection BP is supplied in 2 mL ampoules, boxes of 10.

Fentanyl Injection BP is also supplied in:
- 5 mL single use glass vials, boxes of 10,
- 20 mL single use glass vials, boxes of 5,
- 50 mL Pharmacy Bulk Vials, boxes of 1.

Do not use Fentanyl Injection BP if:

- your doctor did not prescribe it for you
- you are allergic to fentanyl or any of the other ingredients in Fentanyl Injection BP
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

To prevent breathing problems in the newborn baby, fentanyl should not be injected into a vein (intravenous use) during labour or cesarean section before the umbilical cord has been cut. Injection around the spinal cord (epidural use), however, is permitted.

Fentanyl Injection BP should not be injected around the spinal cord (epidural use) if there is shock, severe bleeding, systemic infection, or infection around the injection site. This use should also be avoided if you bleed easily or you are taking a blood-thinner.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Fentanyl Injection BP. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have past or current depression
- suffer from chronic or severe constipation
- are an elderly person
- have a condition with any part of your body, such as your heart, lung, liver, or thyroid
- have problems with your adrenal or prostate gland
- are taking any medication, such as blood thinners, and/or pain killers
- are pregnant or planning to become pregnant
- have a known allergic reaction to this drug or any other pain medications or any other general anesthetics
- have had a head injury (history and/or current), or if you experience difficulties breathing
- suffer from migraines
- have severe kidney, liver, lung disease
- have heart disease
- have low blood pressure
- have, or had in the past, hallucinations or other severe mental problems

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery:
Opioids can be transferred to your baby while still in the womb, or through breast milk. Fentanyl Injection BP can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Fentanyl Injection BP outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking Fentanyl Injection BP, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Fentanyl Injection BP. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Fentanyl Injection BP. Fentanyl Injection BP can cause:

- drowsiness
- dizziness or
- 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 Fentanyl Injection BP.

Serotonin Syndrome: Fentanyl Injection BP 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 Fentanyl Injection BP 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.

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

The following may interact with Fentanyl Injection BP:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Fentanyl Injection BP. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Fentanyl Injection BP
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take Fentanyl Injection BP with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- anti-fungal drugs (used to treat fungal infections)
- anti-retroviral drugs (used to treat viral infections)
- some heart medication (such as beta blockers)
- tranquilizers
- grapefruit juice
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

Your doctor should tell you what medication you may or may not use after your surgery or childbirth.

Before taking Fentanyl Injection BP, tell your doctor about any other medications that you are using including certain antidepressants (selective serotonin reuptake inhibitors (SSRI) and serotonin/norepinephrine reuptake inhibitors (SNRI).

After surgery – Side effects and what to do with them:

In rare cases, muscle stiffness and swollen face have been reported. Call your doctor if you have these conditions.

Since Fentanyl Injection BP are commonly used together with general anesthetics and other drugs, other side effects may occur.

This is not a complete list of side effects. For any unexpected effects while taking Fentanyl Injection BP, contact your doctor or pharmacist.

How to take Fentanyl Injection BP:

Fentanyl Injection BP can only be used by a doctor in a facility with life-saving equipment.

Usual Starting Dose:

Your dose is tailored/personalized just for you. The dose given to you by your doctor will depend on such factors as how much you weigh, your current health status, any diseases you may currently have, and the kind of surgical procedure you will be undergoing.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Fentanyl Injection BP for up to 7 days. If you need to take Fentanyl Injection BP for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need Fentanyl Injection BP. Be sure to use Fentanyl Injection BP only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Fentanyl Injection BP tell your doctor immediately.

Stopping your Medication

If you have been taking Fentanyl Injection BP for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking Fentanyl Injection BP. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations

- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Fentanyl Injection BP.

Overdose:

If you think you have taken too much Fentanyl Injection BP contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:

If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using Fentanyl Injection BP?

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

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Fentanyl Injection BP.

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.	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea.			✓
High blood pressure: headache, dizziness.			✓
Difficulty Urinating			✓

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

Storage:

- **Keep unused or expired Fentanyl Injection BP in a secure place to prevent theft, misuse or accidental exposure.**
- Keep out of the reach of children.
- Store between 15 and 30°C. Protect from light. Protect from freezing. Discard unused portion.
- **Keep Fentanyl Injection BP under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Fentanyl Injection BP, get emergency help right away.**

Disposal:

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

If you want more information about Fentanyl Injection BP:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp ; or by calling SteriMax Inc. at 1-800-881-3550.

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