PRODUCT MONOGRAPH

[N]ratio-FENTANYL

Fentanyl Transdermal System

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	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Patch Five strengths with 2.063, 4.125, 8.25, 12.375 and 16.5 mg fentanyl per patch, delivering 12, 25, 50, 75, 100 mcg/h fentanyl respectively for 72 hours	None

INDICATIONS AND CLINICAL USE

Adults

ratio-FENTANYL (fentanyl transdermal system) is indicated in the management of persistent, moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids, and only in patients:

- who require continuous around-the-clock opioid analgesia for an extended period of time and
- who are already receiving opioid therapy at a total daily dose of at least 60 mg/day Morphine Equivalents.

The initial dose of **ratio-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, **ratio-FENTANYL** should not be used in:

- non-opioid-tolerant patients
- the management of postoperative pain

Special Populations

Pediatrics

The use of **ratio-FENTANYL** in children under 18 years of age is not recommended, as dosage requirements for the safe and efficacious use of fentanyl transdermal system have not been established for this patient population. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal systems.

Elderly and Debilitated Patients

In elderly, cachectic, or debilitated patients, **ratio-FENTANYL** may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance (see **DOSAGE AND ADMINISTRATION**). Therefore, it may be appropriate, according to clinical judgment, to initiate these patients on a lower **ratio-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-naïve (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, ratio-FENTANYL is contraindicated in:

1) patients with acute or postoperative pain, including use in out-patient or day surgeries;
2) patients with mild, intermittent or short duration pain that can otherwise be managed;
3) opioid-naive patients at any dose, including 12 mcg/h dose;
4) situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment; and
5) patients who have acute or severe bronchial asthma.

Because serious or life-threatening hypoventilation could occur, the maximum initiation dose of **ratio-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**).

ratio-FENTANYL is contraindicated in patients who have or are suspected of having paralytic ileus.

ratio-FENTANYL is contraindicated in patients with known hypersensitivity to fentanyl, other opioids, or to the adhesives present in the system.

WARNINGS AND PRECAUTIONS

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: ratio-FENTANYL should not be used in the management of acute or postoperative pain since there is no opportunity for dose titration during short-term use and serious or life-threatening hypoventilation could result. Similarly, ratio-FENTANYL should not be administered to patients who do not have some degree of tolerance to opioid-induced side effects. ratio-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 ratio-FENTANYL dose.

The initial dose of ratio-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 ratio-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 raio-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) .

The use of ratio-FENTANYL in children under 18 years of age is not recommended as dosage requirements for the safe and efficacious use of ratio-FENTANYL have not been established for this patient population. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal systems.

ratio-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.

Since serum fentanyl concentrations decline gradually after system removal, patients who have experienced serious adverse events should be monitored for at least 24 hours after ratio-FENTANYL removal or until the adverse reaction has subsided.

As with other CNS depressants, patients who have received ratio-FENTANYL should be closely monitored especially for signs of respiratory depression until a stable maintenance dose is reached.

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 ratio-FENTANYL patches.

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

Placing ratio-FENTANYL transdermal systems in the mouth, chewing it, swallowing it, or using it in any ways other than indicated may cause choking or overdose that could result in death.

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 **ratio-FENTANYL** dose adjusted if necessary.

External Heat Sources: All patients should be advised to avoid exposing the **ratio-FENTANYL** application site to direct external heat sources, such as heating pads, electric blankets, heated water beds, heat or tanning lamps, hot water bottles, prolonged hot baths, saunas and hot whirlpool spa baths, intensive sunbathing, etc.

Accidental Exposure to ratio-FENTANYL

Serious medical consequences, including death, have occurred when people were accidentally exposed to fentanyl transdermal system. Examples of accidental exposure include transfer of a fentanyl transdermal system while hugging, sharing a bed, or moving a patient.

Disposal of ratio-FENTANYL

ratio-FENTANYL should be kept out of the reach of children before and after use.

Used systems should be folded so that the adhesive side of the system adheres to itself, then flushed down the toilet immediately upon removal. If the matrix from the drug matrix accidentally contacts the skin, the area should be washed with clear water. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet (see **DOSAGE AND ADMINISTRATION** and **SPECIAL HANDLING INSTRUCTIONS**).

Cardiovascular

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

Concomitant Use of Central Nervous System Depressants

When patients are receiving **ratio-FENTANYL**, the dose of additional opioids or other CNS-depressant drugs (including alcohol beverages, benzodiazepines, general anesthetics, muscle relaxants and sedating over-the-counter antihistamines) should be reduced by at least 50%. The concomitant use of CNS depressants may result in hypotension, respiratory depression and profound sedation or coma (see **DRUG INTERACTIONS**).

Concomitant Use of CYP3A4 Inhibitors

The concomitant use of **ratio-FENTANYL** with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir and nefazodone) 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 **ratio-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**).

Potential for Abuse and Diversion

ratio-FENTANYL contains a high concentration of a potent opioid, fentanyl, which along with other opioids of the morphine type has high potential for abuse and associated risk of fatal overdose due to respiratory depression. The high fentanyl content in **ratio-FENTANYL** may be a particular target for abuse and diversion, with alternative routes of administration potentially resulting in overdose from uncontrolled delivery of the opioid.

This risk should be considered when administering, prescribing, or dispensing **ratio-FENTANYL** in situations where the healthcare professional is concerned about increased risk of misuse, abuse or diversion.

Concerns about abuse, addiction and diversion should not prevent the proper management of pain. 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.

Since **ratio-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

Drug Dependence vs Abuse

Fentanyl is an opioid substance and can produce drug dependence similar to that produced by morphine. **ratio-FENTANYL**, therefore, has the potential for abuse. However, tolerance as well as both physical and psychological dependence may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse. Iatrogenic addiction following appropriate opioid administration for relief of severe pain is relatively rare. Physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction.

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

ratio-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.

"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).

Head Injuries and Increased Intracranial Pressure
ratio-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. **ratio-FENTANYL** should be used with caution in patients with brain tumours.

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

ratio-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 **ratio-FENTANYL** may cause increases in the serum amylase concentration.

Psychomotor Impairment
ratio-FENTANYL may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients using **ratio-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, **ratio-FENTANYL** should be used with caution in patients with kidney dysfunction.

Respiratory
Respiratory Depression
As with all potent opioids, some patients may experience significant respiratory depression (including respiratory distress, apnea, bradypnea, hypoventilation, dyspnea) with **ratio-FENTANYL**; caution must be exercised and patients carefully observed for untoward reactions.

While most patients using fentanyl transdermal systems chronically develop tolerance to fentanyl-induced hypoventilation, episodes of slowed respiration may occur at any time during therapy. A small number of patients have experienced clinically significant hypoventilation with fentanyl transdermal system; medical intervention generally was not required in these instances. The incidence of respiratory depression increases as the fentanyl transdermal system dose is increased.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations. 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 **ratio-FENTANYL** (see **DRUG INTERACTIONS** regarding the use of concomitant CNS active drugs). The use of **ratio-FENTANYL** should be monitored by clinical evaluation. 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 **ratio-FENTANYL** may extend beyond the removal of the system (see also **OVERDOSAGE** concerning respiratory depression).

Use in 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
A patient information sheet is included in the package of **ratio-FENTANYL** patches dispensed to the patient.

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

1. Patients should be advised that **ratio-FENTANYL** patches contain fentanyl, an opioid pain medicine similar to morphine, hydromorphone, methadone, oxycodone, and oxymorphone.

2. Patients should be advised that each **ratio-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.

3. Patients should be advised that **ratio-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 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 **ratio-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 might irritate the skin or alter its characteristics.
- Allow the skin to dry completely prior to patch application.

4. Patients should be advised that **ratio-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 **ratio-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.

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

6. 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.

7. Patients should be advised to fold (so that the adhesive side adheres to itself) and immediately flush down the toilet used **ratio-FENTANYL** patches after removal from the skin.

8. Patients should be instructed that, if the matrix from the drug matrix 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.

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

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

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

12. Patients should be advised that **ratio-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.

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

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

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

16. Patients should be advised that **ratio-FENTANYL** contains fentanyl, is a drug with high potential for abuse.

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

18. Patients should be advised that **ratio-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.

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

20. When **ratio-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 flushed down the toilet.

21. 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 **ratio-FENTANYL**.

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

23. 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 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. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of fentanyl transdermal systems during pregnancy. Therefore, **ratio-FENTANYL** should not be used in women of childbearing potential unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use of **ratio-FENTANYL** during childbirth is not recommended because fentanyl passes through the placenta and may cause respiratory depression in the newborn child.

Nursing Women: Fentanyl is excreted in human milk, therefore **ratio-FENTANYL** is not recommended for use in nursing women because of the possibility of effects in their infants.

Pediatrics (<18 years of age): The use of **ratio-FENTANYL** in children under 18 years of age is not recommended, as dosage requirements for the safe and efficacious use of **ratio-FENTANYL** have not been established for this patient population. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal systems.

Elderly and Debilitated Patients: In elderly, cachectic, or debilitated patients, **ratio-FENTANYL** may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance (see **DOSAGE AND ADMINISTRATION**). Therefore, it may be appropriate, according to clinical judgment, to initiate these patients on a lower **ratio-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 **ratio-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 systems have been evaluated in 153 cancer patients and 357 postoperative patients. The duration of fentanyl transdermal system use varied in cancer patients; 56% of patients used fentanyl transdermal systems for over 30 days, 28% continued treatment for more than 4 months, and 10% used fentanyl transdermal systems for more than 1 year. In

cancer patients, fentanyl transdermal systems were administered in doses of 25 mcg/h to 600 mcg/h. Patients with acute pain used fentanyl transdermal systems 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 postoperative 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 systems (25 mcg/h to100 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 systems. During the initial open-label dose-titration and stabilization period of 15 days, a total of 43 patients dropped out; four experienced dyspnea, three nausea and one severe hallucinations.

Following this stabilization period, the nine-day double-blind period began, with patients randomized to either continue the dose of fentanyl transdermal systems achieved during stabilization (n=47) or to switch to placebo (n=48). Rescue morphine was available. The median dose of fentanyl transdermal systems 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 systems 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=301of 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 systems 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 & 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 systems 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 the 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 **ratio-FENTANYL** 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 **ratio-FENTANYL** 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 systems.

Other opioid-related adverse reactions include: nausea, vomiting, constipation, hypotension, bradycardia, somnolence, headache, confusion, hallucination, euphoria, pruritus, sweating, tachycardia, paresthesia, sexual 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.

There have 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 **ratio-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**).

DRUG INTERACTIONS

Overview

Additive Effects of Other CNS Depressants

Hypoventilation, hypotension and profound sedation or coma may occur with the concomitant use of other central nervous system depressants (including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers); skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce additive depressant effects. When combined therapy is contemplated, the dose of each agent should be reduced by at least 50%.

Drug-Drug Interactions

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 **ratio-FENTANYL** is given concurrently with agents that affect CYP3A4 activity.

Coadministration with agents that induce 3A4 activity may reduce the efficacy of **ratio-FENTANYL**. The concomitant use of transdermal fentanyl with ritonavir or other potent 3A4 inhibitors such as ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, diltiazem and erythromycin 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. If the concomitant use of ritonavir and transdermal fentanyl is required, close monitoring is recommended.

The pharmacokinetics of IV fentanyl were not significantly altered by itraconazole (a potent CYP 3A4 inhibitor) given orally for 4 days at 200 mg/day. The clearance of IV fentanyl was reduced by two-thirds by oral ritonavir (one of the most potent CYP 3A4 inhibitors).

MAO Inhibitors

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. Since the safety of fentanyl in this regard has not been established, the use of fentanyl in patients who have received MAO inhibitors during the previous 14-day period is not recommended. Conversely, the use of MAO inhibitors in patients who have received fentanyl in the previous 14-day period is not recommended.

DOSAGE AND ADMINISTRATION

General

ratio-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 ratio-FENTANYL, patients must be tolerant to opioid therapy of comparable potency to that of the intended initiating dose. Use of ratio-FENTANYL in patients who are non-opioid-tolerant, or insufficiently tolerant, may lead to fatal respiratory depression.

Dosing Considerations

ratio-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 dose of **ratio-FENTANYL** which will maintain the patient free of pain at all times. 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 **ratio-FENTANYL** are suggested for the elderly and other groups discussed in **WARNINGS AND PRECAUTIONS**.

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

Initiation of ratio-FENTANYL in patients who are opioid-naive is contraindicated at any dose (see CONTRAINDICATIONS). The initial dose of ratio-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 judgement, to initiate some patients on a lower ratio-FENTANYL dose than that which the conversion tables recommend, including the use of 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, Dose Titration, Titration Dose Increment). The 12 mcg/h dose is not included in the conversion tables (Tables 1.1 and 1.3) 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.

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

Concomitant Use of CYP3A4 Inhibitors

The concomitant use of **ratio-FENTANYL** with potent cytochrome P450 3A4 inhibitors (ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir and nefazodone) 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 **ratio-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 **ratio-FENTANYL** in children under 18 years of age is not recommended as dosage requirements for the safe and efficacious use of fentanyl transdermal system have not been established for this patient population. Life-threatening hypoventilation has been reported in some pediatric patients receiving fentanyl transdermal system.

Adults: Initial Dose Selection

In selecting an initial **ratio-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 **ratio-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 **ratio-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 ratio-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 1.3), 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 **ratio-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 17 hours of **ratio-FENTANYL**, 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.

To convert patients from oral or parenteral opioids to **ratio-FENTANYL**, refer to Table 1.1 (entitled: **From Current Opioid to ratio-FENTANYL: Dose Conversion Guidelines**).

Alternatively, for patients taking opioids or doses not listed in Table 1.1, use Table 1.2 (entitled: **Opioid Analgesics: Parenteral/Oral/Rectal Equianalgesic Potency Conversion**) and Table 1.3 (entitled: **Recommended Initial ratio-FENTANYL Dose Based Upon Daily Oral Morphine Dose).**

Parenteral/Oral/Rectal Equianalgesic Potency Conversion
To convert adult patients from oral or parenteral opioids to **ratio-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.
2. Use Table 1.2 to convert this amount to the equianalgesic oral morphine dose using analgesic equivalency table.
3. Use Table 1.3 to convert this equianalgesic morphine dose to the recommended initial **ratio-FENTANYL** dose. **This conversion recommendation is intentionally conservative to minimize the potential for ratio-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 **ratio-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 **ratio-FENTANYL** is attained.

Elderly, Cachectic, or Debilitated Patients: Initial Dose Selection
In patients from these populations, **ratio-FENTANYL** 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 **ratio-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-naïve (see **CONTRAINDICATIONS**). As with all **ratio-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 **ratio-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 **ratio-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 **ratio-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 **ratio-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 **ratio-FENTANYL** must be individualized according to the pain relief and tolerance of the patient. Appropriate dosage increase 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 ratio-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 ratio-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 ration for calculation of ratio-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 **ratio-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 **ratio-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 **ratio-FENTANYL** dose exceeds 300 mcg/h.

Decreased Dosing or Discontinuation of ratio-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.

Opioid withdrawal symptoms, such as nausea, vomiting, diarrhea, anxiety and shivering, are possible in some patients after conversion or dose decrease.

For patients requiring discontinuation of opioids, a gradual downward titration in small increments, such as in steps of 25%, is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal (**see Dose Adjustment**, Titration Dose Increment).

For all downward titration, it is important to note that it takes 17 hours or more for the fentanyl serum concentration to fall by 50% after system removal.

Safe Use of Tables 1.1, 1.2 and 1.3

To convert patients to another opioid, remove **ratio-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, 1.2 and 1.3 should not be used to convert from ratio-FENTANYL to other opioid therapies. Because the conversion to **ratio-FENTANYL** is conservative, use of Tables 1.1, 1.2 and 1.3 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible.

DOSAGE CONVERSION GUIDELINES FOR FENTANYL TRANSDERMAL SYSTEMS

Table 1.1[1#]
From Current Opioid to ratio-FENTANYL or other Fentanyl Transdermal System (FTS): Dose Conversion Guidelines

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[2]	30-66	67-90	91-111	112-134	135-157	158-179	180-202
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
	↓	↓	↓	↓	↓	↓	↓
Recommended Fentanyl Transdermal System (FTS) Dose	**25 mcg/h**	**37 mgc/h**	**50 mcg/h**	**62 mcg/h**	**75 mcg/h**	**87 mcg/h**	**100 mcg/h**

Alternatively, for adult patients taking opioids or doses not listed in Table 1.1, use the conversion methodology outlined above with Table 1.2

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

[1] **Table 1.1 should not be used to convert from ratio-FENTANYL** and other FTS **to other therapies because this conversion to ratio-FENTANYL and other FTS 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, 1.2, and 1.3).**

[2] Based on clinical experience in patients with chronic pain, the conversion ratio of 10 mg parenteral morphine is equal to approximately 20 – 30 mg oral morphine. In the table above, calculation is based on a 1:2 parenteral to oral dose ratio. For some patients, a 1:3 parenteral to oral dose ratio (10 mg parenteral morphine = 30 mg oral morphine) may be more appropriate. The respective IM/IV morphine equivalents for the various fentanyl transdermal doses with a 1:3 ratio are:

IM/IV morphine (mg/d) at 1:3 parenteral to oral dose ratio	20-44	45-60	61-75	76-90	91-104	105-119	120-134
Recommended FTS Dose	25 mcg/h	37 mcg/h	50 mcg/h	62 mcg/h	75 mcg/h	87 mcg/h	100 mcg/h

[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.

OPIOID ANALGESICS: PARENTERAL/ORAL/RECTAL EQUIANALGESIC POTENCY CONVERSION

Table 1.2:

Opioid Analgesics: Parenteral/Oral/Rectal Equianalgesic Potency Conversion [1]

DRUG	Equivalent Dose (mg) [2] (compared to morphine 10 mg IM)		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine (repeated dosing)	10	20-30 [3]	3-4
Hydromorphone	1.5	7.5	2-4
Anileridine	25	75	2-3
Levorphanol	2	4	4-8
Oxymorphone	1	10 (rectal)	3-4
Methadone[4]	---	---	---
Weak Opioid Agonists:			
Codeine	130	200	3-4
Oxycodone	---	30	2-4
Propoxyphene	50	100	2-4

(1) References:

Foley, K.M., In: Cancer, Principles and Practice of Oncology, 4th Ed., V.T. Devita, Jr., S. Hellman, S.A. Rosenberg (Ed.), J.B. Lippincott Co., Philadelphia, pp. 2417-2448, 1993.

Foley, K. M., New Engl. J. Med. 313: 84-95, 1985.

Aronoff, G.M. and Evans, W.O., In: Evaluation and Treatment of Chronic Pain, 2nd Ed., G.M. Aronoff (Ed.), Williams and Wilkins, Baltimore, pp. 359-368, 1992.

Cherny, N.I. and Portenoy, R.K., In: Textbook of Pain, 3rd Ed., P.D. Wall and R. Melzack (Eds.), Churchill Livingstone, London, pp. 1437-1467, 1994.

(2) Most of these data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain.

(3) The conversion ratio of 10mg parenteral morphine = 20 – 30 mg oral morphine is based on clinical experience in patients with chronic pain.

Reference:

Skaer TL. Practice Guidelines for Transdermal Opioids in Malignant Pain. Drugs: 64(23) 2629-2638, 2004

Berdine HJ, Nesbit SA. Equianalgesic Dosing of Opioids. Journal of Pain & Palliative Care Pharmacotherapy: 20 (4) 79 – 84, 2006.

(4) Extremely variable equianalgesic dose. Patients should undergo personalized titration starting at an equivalent to 1/10 of the morphine dose.

Table 1.3:

Recommended Initial ratio-FENTANYL Dose Based upon Daily Oral Morphine Dose*#

Oral 24-hour morphine (mg/day)		ratio-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 daily oral morphine doses were used as a basis for conversion to a fentanyl transdermal system.

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 ratio-FENTANYL at less than 25 mcg/h; ratio-FENTANYL at any dose is contraindicated in opioid-naive patients (see **CONTRAINDICATIONS**).

Administration

Application of ratio-FENTANYL Patch

ratio-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 **ratio-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 might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to system application.

ratio-FENTANYL should be applied immediately upon removal from the sealed package. The system should not be altered 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 **ratio-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 ratio-FENTANYL Patch
Used systems should be folded so that the adhesive side of the system adheres to itself, then flushed down the toilet immediately upon removal (see **SPECIAL HANDLING INSTRUCTIONS**).

OVERDOSAGE

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

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 **ratio-FENTANYL** and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone. 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.

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.

Minimum effective analgesic serum concentrations of fentanyl in opioid-naive patients range from 0.2 to 1.2 ng/mL; side effects increase in frequency at serum levels above 2 ng/mL. 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

ratio-FENTANYL provides continuous systemic delivery of fentanyl for up to 72 hours. Fentanyl is released along the concentration gradient existing between the matrix of the drug in the patch system and the lower concentration in the skin.

Adults

Absorption**:**

Following initial **ratio-FENTANYL** administration, serum fentanyl concentrations increase gradually, generally levelling 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.

Serum fentanyl concentrations achieved are proportional to the **ratio-FENTANYL** delivery rate (see Table 1.4). 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 1.4:
Pharmacokinetic Parameters of a Fentanyl Transdermal System 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 17 (range 13-22) 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.

Distribution:
The average volume of distribution for fentanyl is 6 L/kg (range 3-8, n=8). The average clearance in patients undergoing various surgical procedures is 46 L/h (range 27-75, n=8). Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13% and 21%.

Metabolism:
Skin does not appear to metabolize fentanyl delivered transdermally. Fentanyl is metabolized primarily in the liver. In humans, the drug is metabolized primarily by N-dealkylation to norfentanyl and other inactive metabolites.

Excretion:
Approximately 75% of an IV 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: In a pharmacokinetic study with non-opioid-tolerant patients, 8 children aged 1.5 to 5 years old on 25 mcg/hr patches were compared to 8 adults on 50 mcg/hr patches. The comparative "dose per mean body weight" i.e. mcg/hr/kg was 1.67 for children vs 0.67 for adults. Mean C_{max} was 50% higher in the children and mean AUC ~25% higher, with both mean T_{max} and mean half-life shorter (approx. 50% and 75% of the adult values, respectively). For 6 of the 8 children, there was no apparent plateau in plasma concentrations. Adjusting for either body weight or body surface area, clearance in pediatric subjects was found to be about 20%-40% higher than in adults.

Analyses of population pharmacokinetics data in pediatrics indicate that the variability in fentanyl AUC and C_{max} values at steady state (C_{ss}) correlated with changes in body surface area (BSA) values observed in subjects. An increase in BSA of 0.1 m^2 is predicted to result in a 4.8% increase in clearance and 4.6% decrease in C_{ss}.

Dosing recommendations for the safe and effective use of **ratio-FENTANYL** 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 **ratio-FENTANYL** 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, **ratio-FENTANYL** 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**).

Hepatic Insufficiency: No data available

Renal Insufficiency: No data available

STORAGE AND STABILITY

ratio-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.

ratio-FENTANYL should be kept out of the reach of children before and after use.

SPECIAL HANDLING INSTRUCTIONS

ratio-FENTANYL should be kept out of the reach of children before and after use.

Do not cut **ratio-FENTANYL** patches.

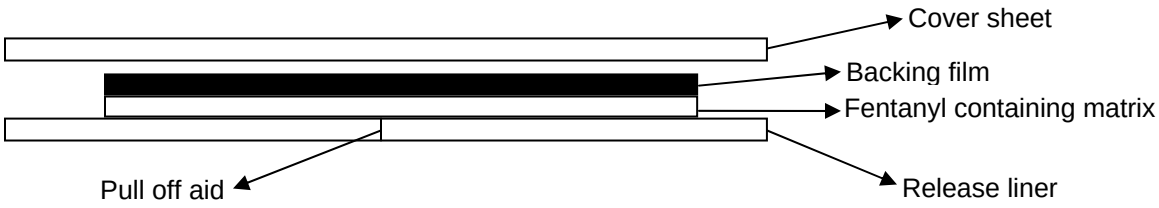
Used systems should be folded so that the adhesive side of the system adheres to itself, then flushed down the toilet immediately upon removal. If the matrix from the drug matrix accidentally contacts the skin, the area should be washed with clear water. Do not use soap, alcohol or other solvents to remove the matrix because they may enhance the drug's ability to penetrate the skin. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their protective pouch and flushed down the toilet.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

ratio-FENTANYL is a rectangular unit comprising a release liner, adhesive drug containing matrix, a backing and a cover sheet. Proceeding from the outer surface toward the surface adhering to the skin, **ratio-FENTANYL** is made up of: 1) the cover sheet which comprises Polyethyleneterepthalate (PET or PETP) foil, with one side siliconized, 2) a backing made of Trespaphane which is in contact with the self adhesive drug containing matrix, 3) a self adhesive drug containing the matrix of Fentanyl, Polybutyltitanate, and Duro-Tak®. 4) 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.



ratio-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, 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. The composition per unit area of all system sizes is identical.

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

Table 1.5

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)
ratio-FENTANYL 12	12.5	2.063	3.75	20 x 20 mm	"fentanyl 12 µg/h"
ratio-FENTANYL 25	25	4.125	7.5	30 x 26mm	"ratio-fentanyl 25 mcg/h"
ratio-FENTANYL 50	50	8.25	15	30 x 51mm	"ratio-fentanyl 50 mcg/h"
ratio-FENTANYL 75	75	12.375	22.5	47.5 x 48mm	"ratio-fentanyl 75 mcg/h"
ratio-FENTANYL 100	100	16.5	30	47.5 x 64mm	"ratio-fentanyl 100 mcg/h"

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

Product Monograph available upon request.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

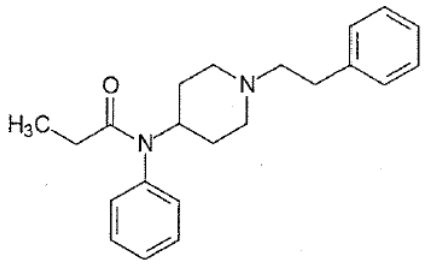
Drug Substance

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

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. ratio-FENTANYL 100 mcg/h, by ratiopharm inc. was compared to Duragesic® 100 mcg/h, by Janssen-Ortho Inc., Canada. The results show that ratio-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)		

* ratio-FENTANYL , ratiopharm inc.

† 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

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 (FTS) 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 (FTS therapy versus placebo) in 46 patients. Doses in these studies varied between 25 and 600 mcg/h. Patients used FTS therapy continuously for up to 866 days; 56% received FTS therapy for over 30 days, 28% continued treatment for more than 4 months and 10% used FTS 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) FTS therapy was accepted by cancer patients, their caregivers and physicians.

Since the introduction of FTS 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 FTS 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 systems 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 these two primary 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 the 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 levelling 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 17 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.

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 the self-adhesive matrix, Duro-Tak®, 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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PART III: CONSUMER INFORMATION

[N]ratio-FENTANYL
fentanyl transdermal system

This leaflet is Part III of a three-part "Product Monograph" published when ratio-FENTANYL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ratio-FENTANYL. Contact your physician or pharmacist if you have any questions about the drug.

Please read this before you start using ratio-FENTANYL patches. Remember, this information does not take the place of your physician's instructions.

- Keep **ratio-FENTANYL** in a safe place away from children and pets. Accidental use by a child or pet is a medical emergency and may result in death. If a child or pet accidentally uses **ratio-FENTANYL**, get emergency help right away.
- Do not use the **ratio-FENTANYL** patch if the patch is cut, damaged or changed in any way.
- Make sure you read the section, **PROPER USE OF THIS MEDICATION.** Follow the instructions and always use a **ratio-FENTANYL** patch the right way. **ratio-FENTANYL** can cause serious breathing problems and death, especially if it is used the wrong way.
- Tell your physician if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines or street drugs.

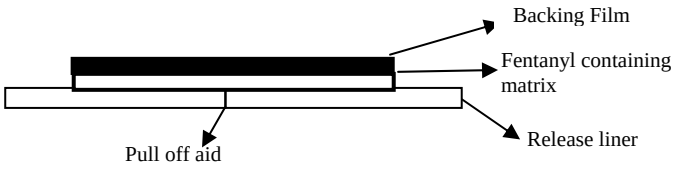
WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ratio-FENTANYL

ratio-FENTANYL is a skin patch that contains fentanyl. **Fentanyl is a very strong opioid narcotic pain medicine that can cause serious and life-threatening breathing problems. Serious and life-threatening breathing problems can happen because of an overdose or if the dose you are using is too high for you. Get emergency medical help immediately if you:**
- have trouble breathing, or have slow or shallow breathing
- have a slow heartbeat
- have severe sleepiness
- have cold, clammy skin
- feel faint, dizzy, confused, or cannot think, walk, or talk normally
- have a seizure
- have hallucinations

ABOUT THIS MEDICATION

What the medication is used for:
Your physician has prescribed **ratio-FENTANYL** to help control the moderate to severe chronic (long-lasting) pain you are experiencing.

What it does:
What is **ratio-FENTANYL**?
ratio-FENTANYL is a thin, adhesive, rectangular patch that is placed on your skin. **ratio-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 ratio-FENTANYL
Because the medicine in **ratio-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 physician may ask you to take additional pain medication until you experience the full benefits of **ratio-FENTANYL.**

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

It is important to let your physician 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 **ratio-FENTANYL** dose. **If you continue to have pain, call your physician.**

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

When it should not be used:
Because life-threatening decreases in breathing rate could occur, ratio-FENTANYL should not be used:
- for the relief of pain following surgery.
- for the relief of pain which is only mild, or expected to last less than several weeks.
- if you have acute or severe bronchial asthma.
- if you have severe difficulty in breathing

For the same reason, do not start on **ratio-FENTANYL** unless you have already been taking a strong opioid medication.

Because constipation is a side-effect of opioids, **ratio-FENTANYL** should not be used if you have a type of intestinal blockage known as "paralytic ileus".

ratio-FENTANYL is not for children under 18 years of age unless your physician has decided otherwise.

Do not use **ratio-FENTANYL** if you know you are allergic to fentanyl, other opioid-type pain medications, or any of the non-medicinal ingredients (see **What the non-medicinal ingredients are**).

What the medicinal ingredient is:
fentanyl

What the nonmedicinal ingredients are:
Backing film: Trespaphane
Self adhesive drug containing the matrix: Fentanyl, Polybutyltitanate, and Duro-Tak®
Peelable release liner: Polyethyleneterepthalate (PET or PETP) foil

What dosage forms it comes in:
ratio-FENTANYL transdermal patch is supplied in cartons containing 5 individually packaged systems.
ratio-FENTANYL 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, 25, 50, 75, and 100 mcg fentanyl per hour respectively for 72 hours.

WARNINGS AND PRECAUTIONS

ratio-FENTANYL patch is not safe for everyone. Tell your physician about all your medical conditions. Before using ratio-FENTANYL be sure to tell your physician if:

- you have any other medical conditions (such as diseases of the heart, lung, brain, liver and kidney),
- you have pancreatitis, or other biliary tract diseases,
- you are pregnant or plan to become pregnant, or are breastfeeding,
- you are taking any other medications **(see INTERACTIONS WITH OTHER MEDICATION)**,
- you have ever had an allergic reaction to any other medication,
- you have a head injury or brain tumour,
- you have a history of drug abuse,
- you have chronic and severe constipation,
- you suffer from alcoholism.

This will help your physician decide whether you should use **ratio-FENTANYL** and what extra care should be taken during its use.

Do not drive a car or operate machinery until you are sure that using the patch does not make you drowsy.

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 physician, who may adjust your dose if necessary. Increased release of fentanyl can also result from direct exposure to heat sources. You should avoid, for example, heating pads, electric blankets, heated water beds, heat lamps, intensive sunbathing, hot water bottles, saunas, hot whirlpool spa baths, and long hot baths.

Tolerance
ratio-FENTANYL may lead to tolerance in the long run. It is therefore possible that your physician will prescribe a higher dose of **ratio-FENTANYL (fentanyl)** after some time to produce the same result.

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

INTERACTIONS WITH THIS MEDICATION

Tell you physician about all the medicines you take. Some medicines may cause serious or life-threatening side effects when used with ratio-FENTANYL. Your physician will tell you if it is safe to take other medicines while you are using **ratio-FENTANYL**.

Know the medicines you take. Keep a list of your medicines to show to your physician and pharmacist.

It is extremely important to avoid alcohol and such medications as tranquilizers and sleeping pills when you are using **ratio-FENTANYL** since their combined effect may cause drowsiness, depressed breathing, low blood pressure and possibly coma.

To avoid any potential drug interactions, be sure to inform your physician when taking any other medications while you are using **ratio-FENTANYL**, including

- certain antifungal drugs (e.g. ketoconazole),
- certain antiviral drugs (e.g. ritonavir),
- some antibiotics (e.g. clarithromycin).
- monoamine (MAO) inhibitors (e.g. phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline),
- over-the-counter medications that may cause drowsiness (e.g. antihistamines),
- muscle relaxants,
- anaesthetics,
- sedatives or hypnotics,
- phenothiazines,
- other opioid pain medication.

Drugs that cause a decrease in the ability of the liver to break down drugs including opioids can result in high levels of opioid in the bloodstream when taken at the same time as the patch is used. These drugs include some anti-fungals, some antibiotics, and some anti-virals. Talk to your physician before starting **ratio-FENTANYL** if you are on one of these drugs.

PROPER USE OF THIS MEDICATION

You should already be taking another strong opioid medication before begin using **ratio-FENTANYL** patches.

Your physician will determine the strength of **ratio-FENTANYL** you need based on your own particular needs. Do not change your dose without consulting your physician. Do not wear more than one **ratio-FENTANYL** patch at a time, unless your physician tells you to do so. Each patch can be used for up to 72 hours (3 days).

Do not stop using **ratio-FENTANYL** suddenly (see **Discontinuation of ratio-FENTANYL**).

Do not use **ratio-FENTANYL** if the pouch is torn upon purchasing, or if the patch is cut, damaged, or changed in any way.

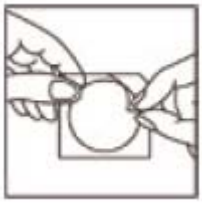
Where to apply ratio-FENTANYL

Select a **dry**, non-hairy area on your chest, back, flank or upper arm. If the area you choose has body hair, clip (do not shave) the hair close to the skin with scissors.

Do **not** put the patch on skin that is excessively oily, burned, broken out, cut, irritated or damaged in any way. If you need to clean the skin where the patch will be applied, use only clear water. Soaps, oils, lotions, alcohol or other products may irritate the skin under the patch.

How to apply ratio-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 the edges down with first aid tape. If problems with the patch not sticking persist, cover the patch with Bioclusive™ or Tegaderm™. These are special see-through adhesive dressings. Never cover a **ratio-FENTANYL** patch with any other bandage or tape.

In the event that the patch falls off before 3 days or 72 hours, discard it (See **Disposing of ratio-FENTANYL**.) and put a new one on at a different skin site. Be sure to let your physician 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 physician).

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.

Step 6.
After wearing the patch for 3 days, or as directed by your physician, remove it (see **Disposing of ratio-FENTANYL**). 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.

Water and ratio-FENTANYL

You can bathe, swim, or take a warm shower while you are wearing **ratio-FENTANYL**. If the patch falls off, discard the patch properly (see **Disposing of ratio-FENTANYL Patch**) 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 physician 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 physician).

Disposing of ratio-FENTANYL Patch

Before putting on a new ratio-FENTANYL patch, remove the patch you have been wearing. Fold the used patch in half so the sticky side sticks to itself, and flush down the toilet immediately. A used ratio-FENTANYL patch can be very dangerous for, or even lead to death in babies, children, pets and adults who have not been prescribed ratio-FENTANYL as considerable amount of drug remains in the patch after use. Do not put used ratio-FENTANYL patches in a trash can.

Wash your hands, with water only, after disposing 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 flush down the toilet. Do not flush the pouch or protective liner.

ratio-FENTANYL contains fentanyl, a drug with a high potential for abuse. Your discarded patches contain a considerable amount of drug, and flushing is an effective way to prevent theft or misuse by others.

Safety and handling
Do not cut, damage or chew ratio-FENTANYL.

ratio-FENTANYL will not work properly, or may not be safe, if it is damaged in any way and may lead to life-threatening consequences.

Do not let anyone else use your ratio-FENTANYL. A ratio-FENTANYL patch must be used only on the skin of the person for whom it was prescribed. ratio-FENTANYL contains fentanyl, a drug with a high potential for abuse. Your patches must be protected from theft or misuse in the home or work environment.

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 that person 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.

Do not exceed the dose recommended by your physician.

Overdose

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

The most important sign of overdose is suppressed breathing. If a person is breathing abnormally slowly or weakly, remove the patch and seek emergency medical care immediately. Meanwhile, keep the person awake by talking or by shaking him/her every now and then.

Other signs of **ratio-FENTANYL** overdose may include tiredness, extreme sleepiness or sedation; inability to think, talk or walk normally; and feeling faint, dizzy or confused, seizure and hallucination.

In the event of overdosage, contact your physician, hospital emergency department or regional Poison Control Centre.

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 **PROPER USE OF THIS MEDICATION**).

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, **ratio-FENTANYL** may cause unwanted effects. Most unwanted effects appear during the first month of treatment. These effects may be more pronounced if you have a fever. If you develop a fever while using the patch, contact your physician right away.

The most frequently reported unwanted effects are nausea, vomiting, tiredness, constipation, sweating, dizziness, headache, dry mouth, confusion, depression and skin irritation at the application site.

Slowed breathing has been reported by a small number of patients using **ratio-FENTANYL**. If this occurs, seek emergency medical care immediately.

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 **ratio-FENTANYL**, or converting from **ratio-FENTANYL** to another opioid. Contact your physician if you experience these symptoms when switching to or from **ratio-FENTANYL**.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Serious and life-threatening breathing problems can happen because of an overdose or if the dose you are using is too high for you (see **Overdose**). If breathing problems develop, seek emergency medical care immediately.

There have been very rare reports of serious allergic reactions, such as Stevens-Johnson syndrome (rash and fever or sore eyes/mouth), airway constriction, swelling, and anaphylactic shock. In one case, it was the patient caretaker who experienced the allergic reaction, from applying the patch to the patient. If these symptoms develop, contact your physician immediately.

There have been rare reports of seizures (convulsions) in people using ratio-FENTANYL. If you notice anything unusual, please contact your physician immediately.

This is not a complete list of side effects. For any unexpected effects while taking* ratio-FENTANYL*, contact your physician or pharmacist.

HOW TO STORE IT

KEEP ratio-FENTANYL OUT OF THE REACH OF CHILDREN.

Keep **ratio-FENTANYL** in its protective pouch until you are ready to use it. Store **ratio-FENTANYL** between 15° and 25°C. Do not refrigerate or freeze. Remember, the inside of your car can reach temperatures much higher than 25°C (77°F) on a sunny day.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healtcanada.gc.ca/medeffect
By email: Canada Vigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture A.L. 0701C
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, ratiopharm inc., at: 1-800-337-2584

This leaflet was prepared by ratiopharm inc.

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