Fentanyl

Class: Analgesic, Opioid; General Anesthetic

Indications: Injection: Relief of pain, preoperative medication, adjunct to general or regional anesthesia

Transdermal patch (eg, Duragesic®): Management of persistent moderate-to-severe chronic pain in opioid-tolerant patients when around-the-clock analgesia is needed for an extended period of time

Note: "Opioid-tolerant" patients are defined as patients who are taking at least:

Oral morphine 60 mg/day, **or**

Transdermal fentanyl 25 mcg/hour, **or**

Oral oxycodone 30 mg/day, **or**

Oral hydromorphone 8 mg/day, **or**

Oral oxymorphone 25 mg/day, **or**

Equianalgesic dose of another opioid for at least 1 week

Available dosage form in the hospital: Injection, solution, as citrate [strength expressed as base]: 0.05 mg/mL (2 mL, 10 mL); 0.25 mg/ 5mL.

Patch, transdermal, as base: 12 [delivers 12.5 mcg/hr]; 50 [delivers 50 mcg/hr]; 100 [delivers 100 mcg/hr]

Trade Names:

Dosage: **Note:** Ranges listed may not represent the maximum doses that may be required in all patients. Doses and dosage intervals should be titrated to pain relief/prevention. Monitor vital signs routinely. Single I.M. doses have duration of 1-2 hours, single I.V. doses last 0.5-1 hour.

Surgery:

Premedication: I.M., slow I.V.: 50-100 mcg/dose 30-60 minutes prior to surgery

Adjunct to regional anesthesia: Slow I.V.: 25-100 mcg/dose over 1-2 minutes. **Note:** An I.V. should be in place with regional anesthesia so the I.M. route is rarely used but still maintained as an option in the package labeling.

Adjunct to general anesthesia: Slow I.V.:

Low dose: 0.5-2 mcg/kg/dose depending on the indication.

Moderate dose: Initial: 2-20 mcg/kg/dose; Maintenance (bolus or infusion): 1-2 mcg/kg/**hour**. Discontinuing fentanyl infusion 30-60 minutes prior to the end

of surgery will usually allow adequate ventilation upon emergence from anesthesia. For "fast-tracking" and early extubation following major surgery, total fentanyl doses are limited to 10-15 mcg/kg.

High dose: 20-50 mcg/kg/dose; **Note:** High-dose fentanyl as an adjunct to general anesthesia is rarely used, but is still described in the manufacturer's label.

Pain management: Adults:

I.V. (unlabeled use): Bolus at start of infusion: 1-2 mcg/kg **or** 25-100 mcg/dose; continuous infusion rate: 1-2 mcg/kg/**hour or** 25-200 mcg/hour

Severe (unlabeled use): I.M, I.V.: 50-100 mcg/dose every 1-2 hours as needed; patients with prior opioid exposure may tolerate higher initial doses

Patient-controlled analgesia (PCA) (unlabeled use): I.V.:

Usual concentration: 10 mcg/mL

Demand dose: Usual: 20 mcg; range: 10-50 mcg

Lockout interval: 5-8 minutes

Usual basal rate: ≤50 mcg/hour

Critically-ill patients (unlabeled dose): Slow I.V.: 25-35 mcg (based on ~70 kg patient) **or** 0.35-0.5 mcg/kg every 30-60 minutes as needed (Barr, 2013). **Note:** More frequent dosing may be needed (eg, mechanically-ventilated patients).

Continuous infusion: 50-700 mcg/hour (based on ~70 kg patient) **or** 0.7-10 mcg/kg/**hour** (Barr, 2013)

Intrathecal (I.T.) (unlabeled use; American Pain Society, 2008): **Must be preservative-free.** Doses must be adjusted for age, injection site, and patient's medical condition and degree of opioid tolerance.

Single dose: 5-25 mcg/dose; may provide adequate relief for up to 6 hours

Continuous infusion: Not recommended in acute pain management due to risk of excessive accumulation. For chronic cancer pain, infusion of very small doses may be practical (American Pain Society, 2008).

Epidural (unlabeled use; American Pain Society, 2008): **Must be preservative-free.** Doses must be adjusted for age, injection site, and patient's medical condition and degree of opioid tolerance

Single dose: 25-100 mcg/dose; may provide adequate relief for up to 8 hours

Continuous infusion: 25-100 mcg/hour

Breakthrough cancer pain: Transmucosal: For patients who are tolerant to and currently receiving opioid therapy for persistent cancer pain; dosing should be individually titrated to provide adequate analgesia with minimal side effects. Dose titration should be done if patient requires more than 1 dose/breakthrough pain episode for several consecutive episodes. Patients experiencing >4 breakthrough pain episodes/day should have the dose of their long-term opioid re-evaluated.

Lozenge (Actiq®): Initial dose: 200 mcg; the second dose may be started 15 minutes after completion of the first dose if pain unrelieved. A maximum of 1 additional dose can be given per pain episode; must wait at least 4 hours before treating another episode. Consumption should be limited to ≤4 units/day. Additional requirements suggest need for improved baseline therapy.

Buccal film (Onsolis®): Initial dose: 200 mcg for all patients **Note:** Patients previously using another transmucosal product should be initiated at doses of 200 mcg; do **not** switch patients using any other fentanyl product on a mcg-per-mcg basis.

Dose titration: If titration required, increase dose in 200 mcg increments once per episode using multiples of the 200 mcg film; do not redose within a single episode of breakthrough pain and separate single doses by ≥2 hours. During titration, do not exceed 4 simultaneous applications of the 200 mcg films (800 mcg). If >800 mcg required, treat next episode with one 1200 mcg film (maximum dose: 1200 mcg). Once maintenance dose is determined, all other unused films should be disposed of and that strength (using a single film) should be used. During any pain episode, if adequate relief is not achieved after 30 minutes following buccal film application, a rescue medication (as determined by healthcare provider) may be used.

Maintenance: Determined dose applied as a single film once per episode and separated by ≥2 hours (dose range: 200-1200 mcg); limit to 4 applications/day. Consider increasing the around-the-clock opioid therapy in patients experiencing >4 breakthrough pain episodes/day.

Buccal tablet (Fentora®): Initial dose: 100 mcg; a second 100 mcg dose, if needed, may be started 30 minutes after the start of the first dose. **Note:** For patients previously using the transmucosal lozenge (Actiq®), the initial dose should be selected using the conversions listed below (maximum: 2 doses per breakthrough pain episode every 4 hours).

Dose titration, if required, should be done using multiples of the 100 mcg tablets. Patient can use two 100 mcg tablets (one on each side of mouth). If that dose is not successful, can use four 100 mcg tablets (two on each side of mouth). If titration requires >400 mcg/dose, then use 200 mcg tablets. **Note:** Buccal tablet may be administered sublingually once an effective maintenance dose has been established.

Conversion from lozenge to buccal tablet (Fentora®):

Lozenge dose 200-400 mcg, then buccal tablet 100 mcg

Lozenge dose 600-800 mcg, then buccal tablet 200 mcg

Lozenge dose 1200-1600 mcg, then buccal tablet 400 mcg

Note: Four 100 mcg buccal tablets deliver approximately 12% and 13% higher values of C_{max} and AUC, respectively, compared to one 400 mcg buccal tablet. To prevent confusion, patient should only have one strength available at a time. Using more than four buccal tablets at a time has not been studied.

Nasal spray (Lazanda®):

Initial dose: 100 mcg (one 100 mcg spray in one nostril) for all patients. **Note:** Patients previously using another fentanyl product should be initiated at a dose of 100 mcg; do not convert patients from other fentanyl products to Lazanda® on a mcg-per-mcg basis.

Dose titration: If pain is relieved within 30 minutes, that same dose should be used to treat subsequent episodes. If pain is unrelieved, may increase to a higher dose using the recommended titration steps. **Must wait at least 2 hours before treating another episode with nasal spray.** Dose titration steps: If no relief with 100 mcg dose, increase to 200 mcg dose per episode (one 100 mcg spray in each nostril); if no relief with 200 mcg dose, increase to 400 mcg per episode (one 400 mcg spray); if no relief with 400 mcg dose, increase to 800 mcg dose per episode (one 400 mcg spray in each nostril). **Note:** Single doses >800 mcg have not been evaluated. There are no data supporting the use of a combination of dose strengths.

Maintenance dose: Once maintenance dose for breakthrough pain episode has been determined, use that dose for subsequent episodes. For pain that is not relieved after 30 minutes of Lazanda® administration or if a separate breakthrough pain episode occurs within the 2 hour window before the next Lazanda® dose is permitted, a rescue medication may be used. Limit Lazanda® use to ≤4 episodes of breakthrough pain per day. If response to maintenance dose changes (increase in adverse reactions or alterations in pain relief), dose readjustment may be necessary. If patient is experiencing >4 breakthrough pain episodes/day, consider increasing the around-the-clock, long-acting opioid therapy; if long-acting opioid therapy dose is altered, re-evaluate and retitrate Lazanda® dose as needed.

Sublingual spray (Subsys®):

Initial dose: 100 mcg for all patients. If pain is unrelieved, 1 additional 100 mcg dose may be given 30 minutes after administration of the first dose. A maximum of 2 doses can be given per breakthrough pain episode; must wait at least 4 hours before treating another episode. **Note:** Patients must remain on around-the-clock opioids during use. Patients previously using other

fentanyl products should be initiated at a dose of 100 mcg; do not convert patients from any other fentanyl product (transmucosal, transdermal, or parenteral) to Subsys® on a mcg-per-mcg basis.

Dose titration: If pain is relieved within 30 minutes, that same dose should be used to treat subsequent episodes and no titration is necessary. If pain is unrelieved, may increase to a higher dose using the recommended titration steps. Goal is to determine the dose that provides adequate analgesia (with tolerable side effects) using a single dose per breakthrough pain episode. For each breakthrough pain episode, if pain unrelieved after 30 minutes only 1 additional dose using the same strength may be given (maximum: 2 doses per breakthrough pain episode). **Must wait at least 4 hours before treating another episode with Subsys®.**

Dose titration steps: If no relief with 100 mcg dose, increase to 200 mcg dose per episode (one 200 mcg unit); if no relief with 200 mcg dose, increase to 400 mcg per episode (one 400 mcg unit); if no relief with 400 mcg dose, increase to 600 mcg dose per episode (one 600 mcg unit); if no relief with 600 mcg dose, increase to 800 mcg dose per episode (one 800 mcg unit); if no relief with 800 mcg dose, increase to 1200 mcg dose per episode (two 600 mcg units); if no relief with 1200 mcg dose, increase to 1600 mcg per episode (two 800 mcg units).

Maintenance dose: Once maintenance dose for breakthrough pain episode has been determined, use that dose for subsequent episodes. If occasional episodes of unrelieved breakthrough pain occur following 30 minutes of Subsys® administration, 1 additional dose using the same strength may be administered (maximum: 2 doses per breakthrough pain episode); patient must wait 4 hours before treating another breakthrough pain episode with Subsys®. Once maintenance dose is determined, limit Susbsys™ use to ≤4 episodes of breakthrough pain per day. If response to maintenance dose changes (increase in adverse reactions or alterations in pain relief), dose readjustment may be necessary. If patient is experiencing >4 breakthrough pain episodes/day, consider increasing the around-the-clock, long-acting opioid therapy.

Sublingual tablet (Abstral®):

Initial dose:

U.S. labeling: 100 mcg for all patients; if pain is unrelieved, a second dose may be given 30 minutes after administration of the first dose. A maximum of 2 doses can be given per breakthrough pain episode; must wait at least 2 hours before treating another episode.

Canadian labeling: 100 mcg for all patients; if pain is unrelieved 30 minutes after administration of Abstral™, an alternative rescue medication (other than Abstral™) may be given. Administer only 1 dose of

Abstral™ per breakthrough pain episode; must wait at least 2 hours before treating another episode.

Note: Patients previously using another fentanyl product should be initiated at a dose of 100 mcg; do not convert patients from other fentanyl products to Abstral® on a mcg-per-mcg basis.

Dose titration: If titration required, increase in 100 mcg increments (up to 400 mcg) over consecutive breakthrough episodes. If titration requires >400 mcg/dose, increase in increments of 200 mcg, starting with 600 mcg dose. During titration, patients may use multiples of 100 mcg and/or 200 mcg tablets for any single dose; do not exceed 4 tablets at one time; safety and efficacy of doses >800 mcg have not been evaluated.

Maintenance dose: Once maintenance dose for breakthrough pain episode has been determined, use only 1 tablet in the appropriate strength per episode; if pain is unrelieved with maintenance dose:

U.S. labeling recommendations: A second dose may be given after 30 minutes; maximum of 2 doses/episode of breakthrough pain; separate treatment of subsequent episodes by ≥2 hours; limit treatment to ≤4 breakthrough episodes/day.

Canadian labeling recommendations: Administer alternative rescue medication after 30 minutes; maximum of 1 Abstral™ dose/episode of breakthrough pain; separate treatment of subsequent episodes by ≥2 hours; limit treatment to ≤4 breakthrough episodes/day.

Consider increasing the around-the-clock long-acting opioid therapy in patients experiencing >4 breakthrough pain episodes/day; if long-acting opioid therapy dose altered, re-evaluate and retitrate Abstral® dose as needed

Chronic pain management: Children ≥2 years and Adults (opioid-tolerant patients): Transdermal patch (Duragesic®):

Initial: To convert patients from oral or parenteral opioids to transdermal patch, a 24-hour analgesic requirement should be calculated (based on prior opioid use). Using the tables, the appropriate initial dose can be determined. The initial fentanyl dosage may be approximated from the 24-hour morphine dosage equivalent and titrated to minimize adverse effects and provide analgesia. With the initial application, the absorption of transdermal fentanyl requires several hours to reach plateau; therefore transdermal fentanyl is inappropriate for management of acute pain. Change patch every 72 hours.

Conversion from continuous infusion of fentanyl: In patients who have adequate pain relief with a fentanyl infusion, fentanyl may be converted to transdermal dosing at a rate equivalent to the intravenous rate. A two-step taper of the infusion to be completed over 12 hours has been recommended (Kornick, 2001) after the patch is

applied. The infusion is decreased to 50% of the original rate six hours after the application of the first patch, and subsequently discontinued twelve hours after application.

Titration: Short-acting agents may be required until analgesic efficacy is established and/or as supplements for "breakthrough" pain. The amount of supplemental doses should be closely monitored. Appropriate dosage increases may be based on daily supplemental dosage using the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/hour increase in fentanyl dosage.

Frequency of adjustment: The dosage should not be titrated more frequently than every 3 days after the initial dose or every 6 days thereafter. Patients should wear a consistent fentanyl dosage through two applications (6 days) before dosage increase based on supplemental opioid dosages can be estimated. **Note:** Upon discontinuation, ~17 hours are required for a 50% decrease in fentanyl levels.

Frequency of application: The majority of patients may be controlled on every 72-hour administration; however, a small number of patients require every 48-hour administration.

Dose conversion guidelines for transdermal fentanyl (see tables).

Note: U.S. and Canadian dose conversion guidelines differ. Consult appropriate table.

U.S. Labeling: Dose Conversion Guidelines: Recommended Initial Duragesic® Dose Based Upon Daily Oral Morphine Dose[1,2]

Oral 24-Hour Morphine (mg/day)	**Duragesic® Dose[3] (mcg/h)**
[1]The table should NOT be used to convert from transdermal fentanyl (Duragesic®) to other opioid analgesics. Rather, following removal of the patch, titrate the dose of the new opioid until adequate analgesia is achieved.	
[2]Recommendations are based on U.S. product labeling for Duragesic®.	
[3]Pediatric patients initiating therapy on a 25 mcg/hour Duragesic® system should be opioid-tolerant and receiving at least 60 mg oral morphine equivalents per day.	
60-134	25
135-224	50
225-314	75
315-404	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

U.S. Labeling: Dose Conversion Guidelines[1,2]

Current Analgesic	Daily Dosage (mg/day)			
[1]The table should NOT be used to convert from transdermal fentanyl (Duragesic®) to other opioid analgesics. Rather, following removal of the patch, titrate the dose of the new opioid until adequate analgesia is achieved.				
[2]Recommendations are based on U.S. product labeling for Duragesic®.				
Morphine (I.M./I.V.)	10-22	23-37	38-52	53-67
Oxycodone (oral)	30-67	67.5-112	112.5-157	157.5-202
Codeine (oral)	150-447	-	-	-
Hydromorphone (oral)	8-17	17.1-28	28.1-39	39.1-51
Hydromorphone (I.V.)	1.5-3.4	3.5-5.6	5.7-7.9	8-10
Meperidine (I.M.)	75-165	166-278	279-390	391-503
Methadone (oral)	20-44	45-74	75-104	105-134
Fentanyl transdermal recommended dose (mcg/h)	**25 mcg/h**	**50 mcg/h**	**75 mcg/h**	**100 mcg/h**

Canadian Labeling: Dose Conversion Guidelines (Adults): Recommended Initial Duragesic® MAT Dose Based Upon Daily Oral Morphine Dose[1,2]

Oral 24-Hour Morphine (Current Dose in mg/day)	Duragesic® MAT Dose (Initial Dose in mcg/h)
[1]The table should NOT be used to convert from transdermal fentanyl (Duragesic® MAT) to other opioid analgesics. Rather, following removal of the patch, titrate the dose of the new opioid until adequate analgesia is achieved.	
[2]Recommendations are based on Canadian product labeling for Duragesic® MAT.	
Note: The 12 mcg/hour dose included in this table is to be used for incremental dose adjustment and is generally not recommended for initial dosing, except for patients in whom lower starting doses are deemed clinically appropriate.	
45-59	12
60-134	25
135-179	37

Canadian Labeling: Dose Conversion Guidelines (Adults): Recommended Initial Duragesic® MAT Dose Based Upon Daily Oral Morphine Dose[1,2]

Oral 24-Hour Morphine (Current Dose in mg/day)	Duragesic® MAT Dose (Initial Dose in mcg/h)
180-224	50
225-269	62
270-314	75
315-359	87
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

Canadian Labeling: Dosing Conversion Guidelines (Adults)[1,2]

Current Analgesic	Daily Dosage (mg/day)

[1]The table should NOT be used to convert from transdermal fentanyl (Duragesic® MAT) to other opioid analgesics. Rather, following removal of the patch, titrate the dose of the new opioid until adequate analgesia is achieved.

[2]Recommendations are based on Canadian product labeling for Duragesic® MAT.

[3]Morphine dose conversion based upon I.M to oral dose ratio of 1:3.

Canadian Labeling: Dosing Conversion Guidelines (Adults)[1,2]							
Current Analgesic	**Daily Dosage (mg/day)**						
[4]Insufficient data available to provide specific dosing recommendations. Use caution; adjust dose conservatively.							
Morphine[3] (I.M./I.V.)	20-44	45-60	61-75	76-90	n/a[4]	n/a[4]	n/a[4]
Oxycodone (oral)	30-66	67-90	91-112	113-134	135-157	158-179	180-202
Codeine (oral)	150-447	448-597	598-747	748-897	898-1047	1048-1197	1198-1347
Hydromorphone (oral)	8-16	17-22	23-28	29-33	34-39	40-45	46-51
Hydromorphone (I.V.)	4-8.4	8.5-11.4	11.5-14.4	14.5-16.5	16.6-19.5	19.6-22.5	22.6-25.5
Fentanyl transdermal recommended dose (mcg/h)	**25 mcg/h**	**37 mcg/h**	**50 mcg/h**	**62 mcg/h**	**75 mcg/h**	**87 mcg/h**	**100 mcg/h**

Dosing: Renal Impairment

Injection: No dosage adjustment provided in manufacturer's labeling; use with caution.

Transdermal (patch): Degree of impairment (ie, Cl_{cr}) not defined in manufacturer's labeling.

Mild-to-moderate impairment: Initial: Reduce dose by 50%.

Severe impairment: Use not recommended.

Dosing: Hepatic Impairment

Injection: No dosage adjustment provided in manufacturer's labeling; use with caution.

Transdermal (patch):

Mild-to-moderate impairment: Initial: Reduce dose by 50%.

Severe impairment: Use not recommended

Common side effects: Cardiovascular: Bradycardia, edema

Central nervous system: CNS depression, confusion, dizziness, drowsiness, fatigue, headache, sedation

Endocrine & metabolic: Dehydration

Gastrointestinal: Constipation, nausea, vomiting, xerostomia

Local: Application-site reaction erythema

Neuromuscular & skeletal: Chest wall rigidity (high dose I.V.), muscle rigidity, weakness

Ocular: Miosis

Respiratory: Dyspnea, respiratory depression

Miscellaneous: Diaphoresis

Pregnancy Risk Factor: C