

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONSOLIS® safely and effectively. See full prescribing information for ONSOLIS

ONSOLIS (fentanyl buccal soluble film), CII
Initial U.S. Approval: 1968

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; CYTOCHROME P450 3A4 INTERACTION RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME
See full prescribing information for complete boxed warning.

- **Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. ONSOLIS is contraindicated in opioid non-tolerant patients and in management of acute or postoperative pain, including headaches/migraines. (5.1)**
- **Accidental ingestion of ONSOLIS, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal (5.2)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedations, respiratory depression, coma, and death. Reserve concomitant prescribing of ONSOLIS and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS (2.1, 5.5)**
- **When dispensing, do not substitute with any other fentanyl products (5.5)**
- **ONSOLIS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.6)**
- **ONSOLIS is available only through a restricted program, called the TIRF REMS Access Program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program (5.7)**
- **Prolonged use of ONSOLIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)**

-----RECENT MAJOR CHANGES-----

Boxed Warnings	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

-----INDICATIONS AND USAGE-----

ONSOLIS is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg/hour of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking ONSOLIS.

Limitations of Use (1)

- Not for use in opioid non-tolerant patients.

- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency room.
- As a part of the TIRF REMS Access program, ONSOLIS may be dispensed only to outpatients enrolled in the program [see *Warnings and Precautions (5.7)*]. For inpatient administration of ONSOLIS (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

-----DOSAGE AND ADMINISTRATION-----

- Patients must require and use around-the-clock opioids when taking ONSOLIS. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with 200 mcg ONSOLIS in all patients. (2.2)
- Titrate using 200 mcg ONSOLIS film increments (up to a maximum of four 200 mcg films or a single 1200 mcg film) to adequate analgesia without undue side effects. (2.2)
- Maximum is one dose per episode; no more than four doses per day (2.2, 2.3)
- Wait at least 2 hours before treating another episode of breakthrough pain with ONSOLIS (2.2)
- When opioid therapy is no longer required, consider discontinuing ONSOLIS along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.6)

-----DOSAGE FORMS AND STRENGTHS-----

Buccal soluble film in 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1200 mcg dosage strengths as fentanyl base (3)

-----CONTRAINDICATIONS-----

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency department. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of ONSOLIS. (4)

-----WARNINGS AND PRECAUTIONS-----

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue ONSOLIS if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of ONSOLIS in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ONSOLIS in patients with impaired consciousness or coma. (5.13)

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence $\geq 10\%$) were nausea, vomiting, dizziness, dehydration, dyspnea, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Meda Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with ONSOLIS because they may reduce analgesic effect of ONSOLIS or precipitate withdrawal symptoms. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not Recommended. (8.2)
- Renal and Hepatic Impairment: Administer ONSOLIS with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

12/2016

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WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISK FROM CYTOCHROME P450 3A4 INTERACTION; RISK FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious, life-threatening, and/or fatal respiratory depression has occurred in patients treated with ONSOLIS, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of ONSOLIS or following a dose increase. The substitution of ONSOLIS for any other fentanyl product may result in fatal overdose. [see *Warnings and Precautions (5.1)*].

Due to the risk of respiratory depression, ONSOLIS is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. [see *Contraindications (4)*]

Accidental Ingestion

Accidental ingestion of even one dose of ONSOLIS, especially by children, can result in a fatal overdose of fentanyl [see *Warnings and Precautions (5.1)*].

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. ONSOLIS must be kept out of reach of children. [see *Warnings and Precautions (5.2)*]

Cytochrome P450 3A4 Interaction

The concomitant use of ONSOLIS with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving ONSOLIS and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.3), Drug Interactions (7)*].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.4), Drug Interactions (7)*].

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

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of ONSOLIS compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose [see *Dosage and Administration (2.1), Warnings and Precautions (5.5)*]

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to ONSOLIS.
- When dispensing, do not substitute an ONSOLIS prescription for other fentanyl products.

Addiction, Abuse, and Misuse

ONSOLIS exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ONSOLIS, and monitor all patients regularly for the development of these behaviors or conditions [see *Warnings and Precautions (5.6)*].

Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose, ONSOLIS is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program, outpatients, pharmacies, and distributors must enroll in the program [see *Warnings and Precautions (5.7)*]. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of ONSOLIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.8)*].

1 INDICATIONS AND USAGE

ONSOLIS is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant around-the-clock to opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking for one week or longer, around-the-clock medicine consisting of at least: 60 mg oral morphine per day, or at least 25 mcg per hour of transdermal fentanyl, or at least 30 mg oral oxycodone per day, or at least 8 g oral hydromorphone per day, or at least 25 mg oral oxymorphone per day, or at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid for one week or longer. Patients must remain on around-the-clock opioids while taking ONSOLIS.

Limitations of Use

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency department [see *Contraindications (3)*].
- As part of the TIRF REMS Access Program, ONSOLIS may be dispensed only to outpatients enrolled in the program [see *Warnings and Precautions (5.7)*]. For inpatient administration of ONSOLIS (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe ONSOLIS on an outpatient basis must enroll in the TIRF REMS Access Program and comply with the requirements of the REMS to ensure safe use of ONSOLIS [see *Warnings and Precautions (5.7)*].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.6)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with ONSOLIS and adjust the dosage accordingly [see *Warnings and Precautions (5.1)*].
- Instruct patients and caregivers to take steps to store ONSOLIS securely and to properly dispose of unused ONSOLIS as soon as no longer needed [see *Warnings and Precautions (5.2, 5.6)*, *Patient Counseling Information (17)*].
- ONSOLIS is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) [see *Warnings and Precautions (5.5)*].

- ONSOLIS is NOT a generic version of any other oral transmucosal fentanyl product [see *Warnings and Precautions (5.5)*].

2.2 Initial Dosage

Initiate treatment with ONSOLIS for all patients with a single initial dose of 200 mcg film.

- Due to differences in the pharmacokinetic properties and individual variability, even patients switching from other fentanyl containing products to ONSOLIS must start with the 200 mcg dose.

2.3 Titration and Maintenance of Therapy

The objective of dose titration is to identify the individual patient's effective and tolerable dose. The dose of ONSOLIS is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and MUST be determined by dose titration.

From the initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia.

Individually titrate ONSOLIS to a dose that provides adequate analgesia with tolerable side effects. All patients MUST begin treatment using one 200 mcg ONSOLIS film. If adequate pain relief *is not achieved* after one 200 mcg ONSOLIS film, titrate using multiples of the 200 mcg ONSOLIS film (for doses of 400, 600, or 800 mcg). Increase the dose by 200 mcg in each subsequent episode until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Do not use more than four of the 200 mcg ONSOLIS films simultaneously. When multiple 200 mcg ONSOLIS films are used, they should not be placed on top of each other and may be placed on both sides of mouth.

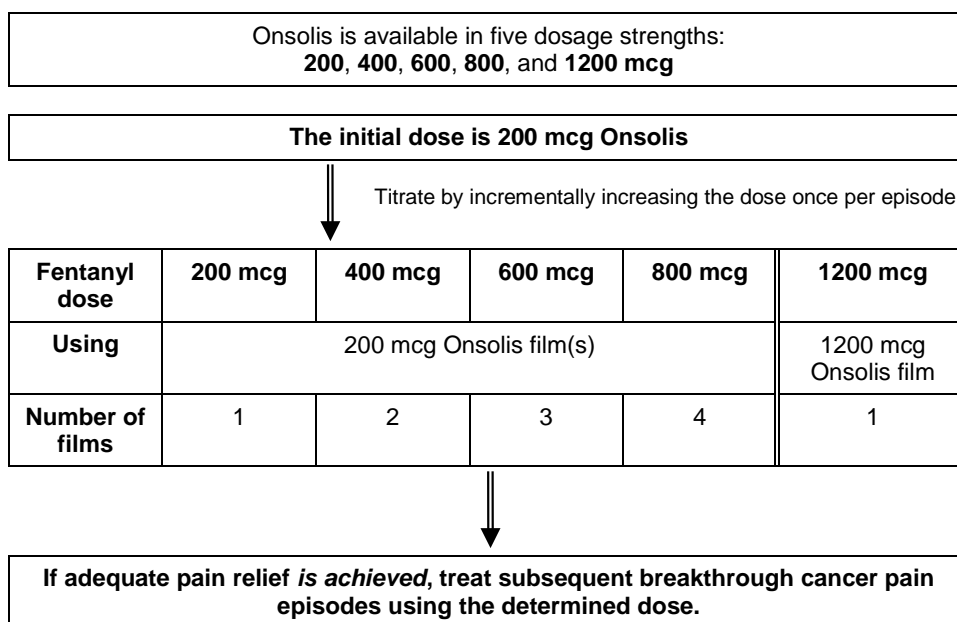
If adequate pain relief *is not achieved* after 800 mcg ONSOLIS (i.e., four 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using one 1200 mcg ONSOLIS film. Doses above 1200 mcg ONSOLIS should not be used.

Once adequate pain relief *is achieved* with a dose between 200 mcg and 800 mcg ONSOLIS, the patient should use or safely dispose of all remaining 200 mcg ONSOLIS films [see *Disposal of ONSOLIS (16.)*]. Patients who require 1200 mcg ONSOLIS, should dispose of all remaining unused 200 mcg ONSOLIS films [see *Disposal of ONSOLIS (16.)*]. The patient should then get a prescription for ONSOLIS films of the dose determined by titration (i.e., 200, 400, 600, 800 or 1200 mcg) to treat subsequent episodes.

Single doses should be separated by at least 2 hours. ONSOLIS should only be used once per breakthrough cancer pain episode, i.e., ONSOLIS should not be redosed within an episode.

During any episode of breakthrough cancer pain, if adequate pain relief *is not achieved* after ONSOLIS, the patient may use a rescue medication (after 30 minutes) as directed by their healthcare provider.

Dose Titration



**Onsolis should only be used once per episode.
Onsolis dosing should be separated by at least 2 hours.**

During any episode, if adequate pain relief *is not achieved* within 30 minutes, the patient may use a rescue medication as directed.

2.4 Dosage Adjustment

During maintenance treatment, if the prescribed dose no longer adequately manages the breakthrough cancer pain episode for several consecutive episodes, increase the dose of ONSOLIS as described in Dose Titration (2.4). Once a successful dose has been found, each episode is treated with a single film. ONSOLIS should be limited to four or fewer doses per day. Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.

2.5 Administration of ONSOLIS

Use the tongue to wet the inside of the cheek or rinse the mouth with water to wet the area for placement of ONSOLIS. Open the ONSOLIS package immediately prior to product use. Place the entire ONSOLIS film near the tip of a dry finger with the printed side facing up and hold in place. Place the printed side of the ONSOLIS film against the inside of the cheek. Press and hold the ONSOLIS film in place for 5 seconds. The ONSOLIS film should stay in place on its own after this period. Liquids may be consumed after 5 minutes.

An ONSOLIS film, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when used as directed [see *Clinical Pharmacology – Pharmacokinetics* (12.3)].

The ONSOLIS film should not be cut or torn prior to use.

The ONSOLIS film will dissolve within 15 to 30 minutes after application. The film should not be manipulated with the tongue or finger(s) and eating food should be avoided until the film is dissolved.

2.6 Discontinuation of ONSOLIS

For patients no longer requiring opioid therapy, consider discontinuing ONSOLIS along with a gradual downward titration of other opioids to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, FENTORA therapy can usually be discontinued immediately. [see *Drug Abuse and Dependence (9.3)*].

2.7 Disposal of ONSOLIS

Patients and their household members must be advised to dispose of any buccal films remaining from a prescription as soon as they are no longer needed. Instructions are included in Patient Counseling Information (17) and in the Medication Guide.

To dispose of any unused ONSOLIS film, remove them from the foil package and flush the film down the toilet. Do not dispose of the ONSOLIS foil packages down the toilet.

If additional assistance is required, call 1-888-227-8725

3 DOSAGE FORMS AND STRENGTHS

ONSOLIS is a buccal soluble film with a white side and a printed white side. The printed side contains a bioadhesive polymer and the active ingredient. Each strength is marked on the printed white side of the film with an identifying number. ONSOLIS is available in the following strengths: [see *How Supplied/Storage and Handling (16)*].

ONSOLIS Dosage Strength (fentanyl base)	Code	Package Color*
200 mcg	2	Bright Blue Aqua
400 mcg	4	Bright Magenta
600 mcg	6	Bright Lime Green
800 mcg	8	Bright Orange
1200 mcg	12	Bright Purple

4 CONTRAINDICATIONS

ONSOLIS is contraindicated in patients:

- Opioid non-tolerant patients: Life threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients [see *Indications and Usage (1)*; *Warnings and Precautions (5.1)*].
- Acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency department [see *Indications and Usage (1)*].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions (5.9)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.14)*]

- Known hypersensitivity (e.g. anaphylaxis) to fentanyl or components of ONSOLIS [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ONSOLIS, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of ONSOLIS.

To reduce the risk of respiratory depression, proper dosing and titration of ONSOLIS are essential [*see Dosage and Administration (2.4)*]. Overestimating the ONSOLIS dosage can result in a fatal overdose with the first dose. The substitution of ONSOLIS for any other fentanyl product may result in fatal overdose [*see Warnings and Precautions (5.5)*].

ONSOLIS could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Accidental ingestion of even one dose of ONSOLIS, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products.

Patients and their caregivers must be informed that ONSOLIS contains a medicine in an amount which can be fatal to a child. Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [*see Patient Counseling Information (17)*].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of ONSOLIS are provided in the ONSOLIS Medication Guide. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of ONSOLIS with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory

depression [see *Warnings and Precautions (5.2)*], particularly when an inhibitor is added after a stable dose of ONSOLIS is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in ONSOLIS treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using ONSOLIS with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ONSOLIS -treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ONSOLIS until stable drug effects are achieved [see *Drug Interactions (7)*].

Concomitant use of ONSOLIS with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using ONSOLIS with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see *Drug Interactions (7)*].

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ONSOLIS with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see *Drug Interactions (7)*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ONSOLIS is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see *Drug Interactions (7)* and *Patient Counseling Information (17)*].

5.5 Risk of Medication Errors

When prescribing, DO NOT convert a patient to ONSOLIS from any other fentanyl products on a mcg per mcg basis from other fentanyl products as ONSOLIS and other fentanyl products are not equivalent on a microgram per microgram basis. Instructions for safely converting patients to ONSOLIS from other fentanyl products are not currently available.

ONSOLIS is not equivalent to all other fentanyl products used to treat breakthrough cancer pain on a mcg per mcg basis. When dispensing ONSOLIS to a patient, DO NOT substitute it for any other fentanyl product

prescription. There are differences in the pharmacokinetics of ONSOLIS relative to other fentanyl products which could potentially result in clinically important differences in the amount of fentanyl absorbed and could result in a fatal overdose. This includes oral, transdermal, or parenteral formulations of fentanyl. Therefore, for opioid-tolerant patients starting treatment for breakthrough cancer pain, the initial dose of ONSOLIS should always be 200 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects. [see *Dosage and Administration (2.1)*]

5.6 Addiction, Abuse, and Misuse

ONSOLIS contains fentanyl, a Schedule II controlled substance. As an opioid, ONSOLIS exposes users to the risks of addiction, abuse, and misuse [see *Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ONSOLIS. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ONSOLIS, and monitor all patients receiving ONSOLIS for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ONSOLIS, but use in such patients necessitates intensive counseling about the risks and proper use of ONSOLIS along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ONSOLIS. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.7 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose [see *Drug Abuse and Dependence (9)*], ONSOLIS is available only through a restricted program called the TIRF REMS Access Program. Under the TIRF REMS Access Program, outpatients, prescribers who prescribe to outpatients, pharmacies, and distributors must enroll in the program. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of ONSOLIS, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access Program are:

- Healthcare professionals who prescribe ONSOLIS must review the prescriber educational materials for the TIRF REMS Access Program, enroll in the program, and comply with the REMS requirements.
- To receive ONSOLIS, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense ONSOLIS must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute ONSOLIS must enroll in the program and distribute only to authorized pharmacies.

Further information, including a list of qualified pharmacies/distributors, is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of ONSOLIS during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [*see Use in Specific Populations (8.1), Patient Counseling Information (17)*].

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of ONSOLIS in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: ONSOLIS-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of ONSOLIS [*see Warnings and Precautions (5.3)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [*see Warnings and Precautions (5.3)*].

Monitor such patients closely, particularly when initiating and titrating ONSOLIS and when ONSOLIS is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.3)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of ONSOLIS with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [*see Drug Interactions (7)*]. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue ONSOLIS if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The

information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

ONSOLIS may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) [see *Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of ONSOLIS. In patients with circulatory shock, ONSOLIS may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ONSOLIS in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ONSOLIS may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ONSOLIS.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of ONSOLIS in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions

ONSOLIS is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in ONSOLIS may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

The fentanyl in ONSOLIS may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during ONSOLIS therapy.

5.16 Risks of Driving and Operating Machinery

ONSOLIS may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of ONSOLIS and know how they will react to the medication.

5.17 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use ONSOLIS with caution in patients with bradyarrhythmias.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression [see *Warnings and Precautions (5.1)*]

- Interactions with Benzodiazepines and other CNS Depressants [see Warnings and Precautions (5.4)]
- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.6)]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.8)]
- Serotonin Syndrome [see Warnings and Precautions (5.10)]
- Adrenal Insufficiency [see Warnings and Precautions (5.11)]
- Severe Hypotension [see Warnings and Precautions (5.12)]
- Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.14)]
- Seizures [see Warnings and Precautions (5.15)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ONSOLIS has been evaluated in 306 opioid tolerant patients with breakthrough cancer pain in the efficacy study and an open-label safety study. The mean duration of therapy was 115 days, with 32 patients treated for more than 1 year.

The most serious adverse reactions associated with all opioids including ONSOLIS are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

Because the clinical trials of ONSOLIS were designed to evaluate safety and efficacy in treating patients with breakthrough pain associated with cancer, all patients were also taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse event among patients who received ONSOLIS for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of ONSOLIS therapy, or cancer-related symptoms. Adverse reactions are included regardless of severity. Table 1 lists, by maximum dose received, adverse reactions with an overall frequency of 5% or greater that occurred during titration. The ability to assign a dose-response relationship to these adverse reactions is limited by the titration schedules used in these studies. Adverse reactions are listed in descending order of frequency within each body system.

Table 1
Adverse Reactions Which Occurred During Titration at a Frequency of ≥5%

System Organ Class, Preferred Term, n (%)	Onsolis Dose (mcg)						Total (N=306)
	200 (N=303)	400 (N=257)	600 (N=207)	800 (N=138)	1200 (N=79)	>1200 (N=9)	
Gastrointestinal Disorders							
Nausea	16 (5)	12 (5)	6 (3)	5 (4)	4 (5)	0	42 (14)
Vomiting	7(2)	9 (4)	8 (4)	2 (1)	0	0	26 (8)
Nervous System Disorders							
Dizziness	5 (2)	5 (2)	6 (3)	2 (1)	4 (5)	0	22 (7)
Somnolence	6 (2)	2 (1)	4 (2)	2 (1)	4 (5)	1 (11)	17 (6)

Table 2 lists, by successful dose, adverse reactions with an overall frequency of $\geq 5\%$ that occurred during long-term treatment (i.e., the double-blind or open-label maintenance periods).

Table 2
Adverse Reactions Which Occurred During Long-Term Treatment at a Frequency of $\geq 5\%$

System Organ Class, Preferred Term, n (%)	Onsolis Dose (mcg)						Total (N=213)
	200 (N=23)	400 (N=59)	600 (N=79)	800 (N=91)	1200 (N=81)	>1200 (N=28)	
Gastrointestinal							
Nausea	2 (9)	6 (10)	8 (10)	12 (13)	26 (32)	4 (14)	56 (26)
Vomiting	1 (4)	5 (8)	9 (11)	8 (9)	23 (28)	3 (11)	45 (21)
Constipation	2 (9)	4 (7)	4 (5)	4 (4)	6 (7)	4 (14)	23 (11)
Diarrhea	1 (4)	1 (2)	4 (5)	4 (4)	10 (12)	0	19 (9)
Dry mouth	1 (4)	4 (7)	3 (4)	2 (2)	3 (4)	1 (4)	14 (7)
Abdominal pain	0	0	3 (4)	1 (1)	7 (9)	1 (4)	11 (5)
General/administration site							
Asthenia	0	6 (10)	3 (4)	8 (9)	7 (9)	4 (14)	28 (13)
Fatigue	2 (9)	6 (10)	1 (1)	7 (8)	7 (9)	3 (11)	25 (12)
Investigations							
Weight decreased	3 (13)	0	2 (3)	5 (5)	5 (6)	1 (4)	15 (7)
Metabolism/nutrition							
Dehydration	1 (4)	4 (7)	6 (8)	5 (5)	10 (12)	3 (11)	28 (13)
Decreased appetite	0	4 (7)	4 (5)	6 (7)	2 (2)	2 (7)	18 (8)
Anorexia	2 (9)	1 (2)	3 (4)	4 (4)	6 (7)	1 (4)	17 (8)
Nervous system							
Dizziness	2 (9)	4 (7)	2 (3)	3 (3)	10 (12)	2 (7)	23 (11)
Headache	2 (9)	1 (2)	3 (4)	9 (10)	7 (9)	0	20 (9)
Somnolence	2 (9)	0	4 (5)	2 (2)	3 (4)	3 (11)	14 (7)
Psychiatric							
Confusional state	1 (4)	0	4 (5)	4 (4)	6 (7)	4 (14)	18 (8)
Depression	0	3 (5)	1 (1)	4 (4)	7 (9)	3 (11)	18 (8)
Insomnia	0	2 (3)	2 (3)	3 (3)	4 (5)	2 (7)	12 (6)
Anxiety	1 (4)	1 (2)	2 (3)	3 (3)	3 (4)	1 (4)	11 (5)
Respiratory							
Dyspnea	3 (13)	4 (7)	3 (4)	8 (9)	6 (7)	3 (11)	26 (12)
Cough	1 (4)	0	3 (4)	5 (5)	6 (7)	1 (4)	15 (7)
Vascular							
Hypotension	0	3 (5)	3 (4)	1 (1)	3 (4)	1 (4)	11 (5)

In a mucositis study, a group of patients (n=7) with Grade 1 oral mucositis and a matched group of control patients (n=7) without oral mucositis were included in a clinical trial designed to support the safety of Onsolis. The adverse event profile was similar in both subsets of patients. There was no evidence that Onsolis caused or worsened oral mucosal irritation or pain in either study group.

The duration of exposure to ONSOLIS varied greatly, and included open-label and double-blind studies. The adverse reactions listed below represent those that were reported by $\geq 1\%$ of patients from two clinical trials (the titration and post-titration periods) while receiving Onsolis. Events are classified by system organ class.

Cardiac disorders: tachycardia

Eye disorders: vision blurred, diplopia

Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, dry mouth, abdominal pain, dyspepsia, dysphagia, abdominal distension, intestinal obstruction, flatulence

General disorders and administration site conditions: asthenia, fatigue, malaise

Injury, poisoning and procedural complications: fall, contusion

Investigations: weight decreased, blood pressure increased

Metabolism and nutrition disorders: dehydration, decreased appetite, anorexia

Nervous system disorders: dizziness, somnolence, headache, lethargy, amnesia, sedation

Psychiatric disorders: confusional state, depression, insomnia, anxiety, hallucination, agitation, mental status changes

Renal and urinary disorders: urinary retention

Respiratory, thoracic and mediastinal disorders: dyspnea, cough

Skin and subcutaneous tissue disorders: pruritus, rash

Vascular disorders: hypotension, hot flush, deep vein thrombosis, hypertension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fentanyl. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin Syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ONSOLIS.

Androgen Deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [*see Clinical Pharmacology (12.2)*].

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with ONSOLIS.

Table 3: Clinically Significant Drug Interactions with ONSOLIS

Inhibitors of CYP3A4	
<i>Clinical Impact:</i>	The concomitant use of ONSOLIS and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of ONSOLIS is achieved [<i>see Warnings and Precautions (5.3)</i>]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease [<i>see Clinical Pharmacology (12.3)</i>], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of ONSOLIS until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the ONSOLIS dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
<i>Examples</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
<i>Clinical Impact:</i>	The concomitant use of ONSOLIS with CYP3A4 inducers can decrease the plasma concentration of fentanyl [<i>see Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have

	developed physical dependence to fentanyl [see <i>Warnings and Precautions (5.3)</i>]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the ONSOLIS dosage until stable drug effects are achieved [see <i>Dosage and Administration (2.4)</i>]. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ONSOLIS dosage reduction and monitor for signs of respiratory depression.
<i>Examples</i>	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor patients for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.4)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see <i>Warnings and Precautions 5.10</i>].
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ONSOLIS if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome [see <i>Warnings and Precautions (5.10)</i>] or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.1)</i>].
<i>Intervention:</i>	The use of ONSOLIS is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	phenelzine, tranlycypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of ONSOLIS and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine,
Muscle Relaxants	
<i>Clinical Impact:</i>	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than

	otherwise expected and decrease the dosage of ONSOLIS and/or the muscle relaxant as necessary.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when ONSOLIS is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with ONSOLIS in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing for ONSOLIS.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [*see Warnings and Precautions (5.2)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. ONSOLIS is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including ONSOLIS, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Animal Data

Fentanyl has been shown to be embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.25 times the 1200 mcg dose of ONSOLIS on a mg/m² basis) and 160 mcg/kg subcutaneously (1.3 times the 1200 mcg dose of ONSOLIS based on a mg/m² basis). There was no evidence of teratogenicity reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 4 times the human dose of 1600 mcg ONSOLIS per pain episode on a mg/m² basis and produced mean steady-state plasma levels that are 3.8 times higher than the mean C_{max} observed following administration of 1200 mcg dose of ONSOLIS in humans.

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ONSOLIS.

Clinical Considerations

Monitor infants exposed to ONSOLIS through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see *Adverse Reactions* (6.2), *Clinical Pharmacology* (12.2), *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

Safety and efficacy of pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Of the 306 opioid tolerant patients with breakthrough cancer pain in clinical studies with ONSOLIS, 98 (32.0%) were 65 years of age or older. There was no difference in the median titrated dose in patients aged 65 years and older compared to those <65 years. No clinically meaningful difference was noted in the safety profile of the group 65 years of age and older as compared to younger patients in ONSOLIS clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger adult population. Therefore, exercise caution when individually titrating ONSOLIS in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of ONSOLIS slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions (5.1)*].

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of Onsolis in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via the human CYP3A4 isoenzyme system and the inactive metabolite is mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

It is recommended that Onsolis be titrated to clinical effect for all patients with special care taken in patients with severe renal or hepatic disease [see *Dosing and Administration (2.3)*, *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ONSOLIS contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

ONSOLIS contains fentanyl, a substance with a high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. ONSOLIS can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.6)*].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include 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, and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient

with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

ONSOLIS, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, 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.

Risks Specific to Abuse of ONSOLIS

ONSOLIS is for buccal route use only. Abuse of ONSOLIS poses a risk of overdose and death. The risk is increased with concurrent abuse of ONSOLIS with alcohol and other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.1)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with ONSOLIS can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

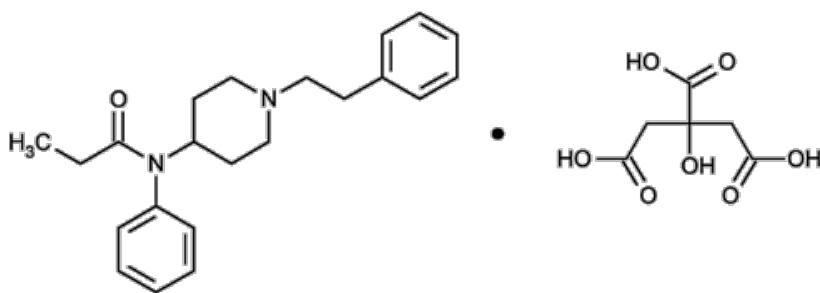
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in ONSOLIS, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

ONSOLIS (fentanyl buccal soluble film) is an oral transmucosal formulation of fentanyl citrate, an opioid agonist, intended for application to the buccal mucosa. ONSOLIS uses the BioErodible Muco Adhesive (BEMA®) bilayer delivery technology which is comprised of water-soluble polymeric films. The active ingredient, fentanyl citrate, is incorporated into the bioadhesive layer, which adheres to the moist buccal mucosa. The amount of fentanyl delivered transmucosally is proportional to the film surface area. It is believed that the inactive layer isolates the bioadhesive layer from the saliva, which may optimize delivery of fentanyl across the buccal mucosa. The chemical name is N-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1). The molecular weight of the free base is 336.5 (the citrate salt is 528.6) and it has the following chemical structure.



Fentanyl citrate is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816.1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The pKa of the tertiary nitrogens are 7.3 and 8.4.

The inactive ingredients in ONSOLIS include: black ink, carboxymethylcellulose, citric acid, hydroxyethyl cellulose, hydroxypropyl cellulose, methylparagen, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, sodium benzoate, sodium hydroxide, sodium saccharin, titanium dioxide, tribasic sodium phosphate, vitamin E acetate, and water. ONSOLIS consists of printed white bioadhesive layer bonded onto a white inactive layer.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ONSOLIS contains fentanyl, an opioid agonist, whose principal therapeutic action is analgesia.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

Effects on the Cardiovascular System

Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Adverse Reactions (6.2)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [*see Adverse Reactions (6.2)*].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. [*see Dosage and Administration (2.3)*].

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [*see Dosage and Administration (2.1, 2.4)*].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [*see Dosage and Administration (2.1, 2.2, 2.4)*].

Respiratory System

All opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may cause rigidity in the muscles of respiration resulting in respiratory difficulties. [*see Warnings and Precautions (5.1)*].

12.3 Pharmacokinetics

Absorption

The absorption pharmacokinetics of fentanyl from ONSOLIS is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Following buccal application of ONSOLIS, the absolute bioavailability of fentanyl was 71%. Approximately 51% of the total dose of ONSOLIS is absorbed from the buccal mucosa. The remaining 49% of the total dose is swallowed with the saliva and then slowly absorbed from the GI tract. Of the swallowed fentanyl, about 20% of the total dose escapes hepatic and intestinal first-pass elimination and becomes systemically available. An ONSOLIS film, if chewed and swallowed, will likely result in lower peak concentrations and lower bioavailability than when consumed as directed.

The absolute bioavailability study also demonstrated similar pharmacokinetics in the subsets of six male and six female adult normal volunteers.

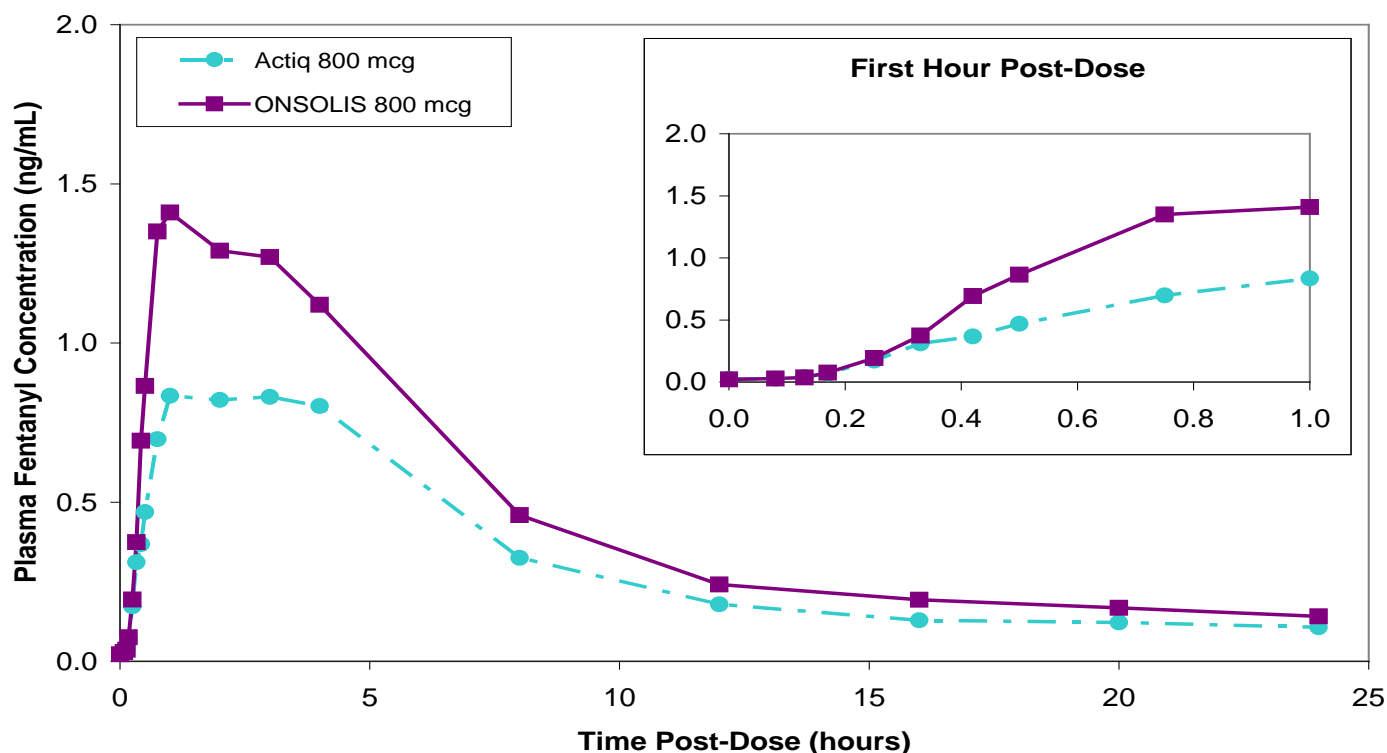
In a study that compared the relative bioavailability of ONSOLIS and Actiq[®] (oral transmucosal fentanyl citrate [OTFC]) in 12 adult normal volunteers, the rate and extent of fentanyl absorption were considerably greater with ONSOLIS [62% greater maximum plasma concentration (C_{max}) and 40% greater systemic exposure (AUC_{inf})] (Table 4 and Figure 1).

Table 4
Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects
Receiving Single Doses of ONSOLIS or Actiq

Pharmacokinetic Parameter*	ONSOLIS (800 mcg)	Actiq (800 mcg)
C_{max} (ng/mL)	1.67 ± 0.75	1.03 ± 0.25
AUC_{inf} (hr·ng/mL)	14.46 ± 5.4	10.30 ± 3.8
T_{first} (min)	9.0 ± 4.8	13.2 ± 10.8
T_{max} (hr)	1.00 (0.75 – 4.00)	2.00 (0.50 – 4.00)

* Data for T_{max} presented as median (range); other data are presented as mean ± SD

Figure 1
Mean Fentanyl Plasma Concentration versus Time Profiles
Following Single Doses of ONSOLIS or Actiq in Healthy Adult Subjects



In another study, dose proportionality across the range of the available dosage strengths of ONSOLIS was demonstrated in a balanced crossover design comparing fentanyl plasma concentrations in three dosage strengths (200, 600, and 1200 mcg) in adult normal volunteers (n=12). Mean fentanyl plasma concentrations following these three doses of ONSOLIS are shown in Table 5. The curves for each dose level are similar in shape with increasing doses producing increasing fentanyl plasma concentrations. C_{max} and AUC_{inf} increased in a manner that is approximately proportional to the ONSOLIS dose administered. The mean C_{max} ranged from 0.38 ng/mL to 2.19 ng/mL over this dose range.

Table 5
Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects
Receiving Single Doses of 200-, 600-, and 1200-mcg of ONSOLIS

Pharmacokinetic Parameter *	Onsolis Dose (mcg)		
	200	600	1200
C _{max} (ng/mL)	0.38 ± 0.07	1.16 ± 0.19	2.19 ± 0.54
AUC _{inf} (hr·ng/mL)	3.46 ± 0.72	11.72 ± 5.29	20.43 ± 4.52

* Based on venous blood samples.

The effect of oral mucositis (Grade 1) on the pharmacokinetic profile of ONSOLIS was studied in a group of patients with cancer, with (n=7) and without (n=7) oral mucositis who were otherwise matched. A single 200 mcg ONSOLIS film was administered, followed by sampling at appropriate intervals. Summary results are presented in Table 6. Application of ONSOLIS on an active site of mucositis was associated with decreases in the C_{max} and AUC_{inf} that are not likely to be clinically relevant. The difference in C_{max} is less than the intersubject variability and dose adjustment is not required.

Table 6
Fentanyl Plasma Pharmacokinetic Parameters in Adult Patients with or without Mucositis
Receiving Single Doses of ONSOLIS

Patient status	C _{max} (ng/mL)	T _{max} (hr) *	AUC ₀₋₄ (hr·ng/mL)
Mucositis	0.47 ± 0.32	1.00 (0.50 – 4.00)	1.14 ± 0.71
No mucositis	0.69 ± 0.54	1.00 (0.50 – 1.50)	1.29 ± 0.87

* Data for T_{max} presented as median (range); other data are presented as mean ± SD

Distribution

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady state (V_{ss}) was 4 L/kg.

Elimination

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies [see *Drug Interactions (7)*].

Excretion

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg). The terminal elimination half-life after ONSOLIS administration is about 14 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of fentanyl have not been conducted.

Mutagenesis

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium* or *E. coli* or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for ONSOLIS (see Section 8.1).

14 CLINICAL STUDIES

The efficacy of ONSOLIS was investigated in a clinical trial in opioid tolerant adult patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in patients with cancer experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for 1 week or longer. All patients were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain.

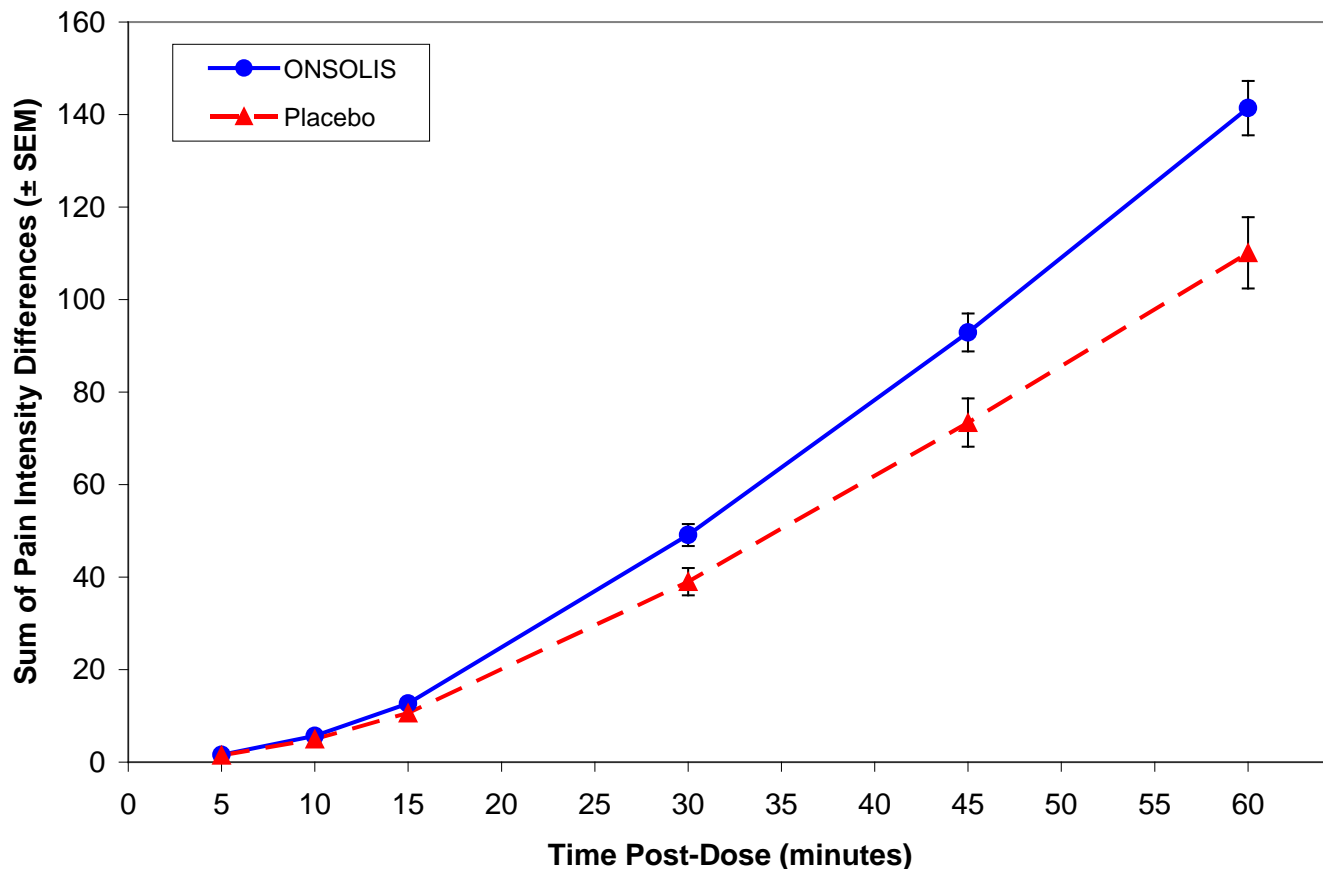
A double-blind, placebo-controlled, crossover study was performed in patients with cancer to evaluate the effectiveness of ONSOLIS for the treatment of breakthrough cancer pain. Open-label titration identified a successful dose of ONSOLIS, within the range of 200 to 1200 mcg. A “successful” dose was defined as a dose in which a patient obtained adequate analgesia with tolerable side effects. Table 6 presents the successful dose for both the double-blind efficacy and open-label safety studies. In the double-blind efficacy study, patients who identified a successful dose were randomized to a sequence of nine treatments; six with the successful dose of ONSOLIS and three with placebo. Of the patients who entered the study, 54 percent achieved a successful dose during the titration phase and 4 percent withdrew for lack of effective pain relief. The final titrated dose of ONSOLIS for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and, therefore, the dose was determined by titration starting at 200 mcg.

Table 7
Dose of ONSOLIS Following Initial Titration

ONSOLIS Dose	Double-blind Efficacy Study Total No. (%) (N=81)
200 mcg	4 (5%)
400 mcg	15 (19%)
600 mcg	23 (28%)
800 mcg	19 (23%)
1200 mcg	20 (25%)

The primary outcome measure, the mean sum of pain intensity differences at 30 minutes (SPID30) for ONSOLIS-treated episodes was statistically significantly higher than for placebo-treated episodes (see Figure 2).

Figure 2
Sum of Pain Intensity Differences (SPID) Following ONSOLIS or Placebo
in Adult Patients with Breakthrough Cancer Pain



16 HOW SUPPLIED/STORAGE AND HANDLING

ONSOLIS is supplied in five dosage strengths. Each film is individually wrapped in a child-resistant, protective foil package. These foil packages are packed 30 per carton.

ONSOLIS is a bilayer film with one white side and one printed white side. The dosage strength of each film is indicated by the code on the printed side of the film, and the dosage strength is marked on the foil package and the 30-film carton. See package and carton for product information.

ONSOLIS Dosage Strength (fentanyl base)	Code	Package Color*	NDC Number
200 mcg	2	Bright Blue Aqua	NDC 0037-5200-30
400 mcg	4	Bright Magenta	NDC 0037-5400-30
600 mcg	6	Bright Lime Green	NDC 0037-5600-30
800 mcg	8	Bright Orange	NDC 0037-5800-30
1200 mcg	12	Bright Purple	NDC 0037-5120-30

* **Colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.**

Store at 20°-25°C (68°-77°F) with excursions permitted between 15°-30°C (59°-86°F) until ready to use (see USP Controlled Room Temperature). Protect ONSOLIS from freezing and moisture. Do not use if the foil package has been opened.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting ONSOLIS or when the dosage is increased, and that it can occur even at recommended dosages [see *Warnings and Precautions (5.1)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Increased Risk of Overdose and Death in Children Due to Accidental Ingestion [see *Warnings and Precautions (5.2)*]

- Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death.
- Inform patients and their caregivers that, in the event that a unit is not completely consumed, it must be properly disposed as soon as possible.
- Instruct patients to take steps to store ONSOLIS securely and to dispose of unused ONSOLIS.
- Instruct patients and caregivers to keep both used and unused ONSOLIS out of the reach of children .

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ONSOLIS is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see *Warnings and Precautions (5.4)*, *Drug Interactions (7)*].

Addiction, Abuse, and Misuse

Inform patients that the use of ONSOLIS, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.6)*]. Instruct patients not to share ONSOLIS with others and to take steps to protect ONSOLIS from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Advise patients of the following information pertaining to the TIRF REMS

- Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive ONSOLIS.
- Allow patients the opportunity to ask questions and discuss any concerns regarding ONSOLIS or the TIRF REMS Access program.
- As required by the TIRF REMS Access program, review the contents of the ONSOLIS Medication Guide with every patient before initiating treatment with ONSOLIS.
- Advise the patient that ONSOLIS is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug.
- Advise the patient that only enrolled healthcare providers may prescribe ONSOLIS.
- Inform the patient that they must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of ONSOLIS.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program [see *Warnings and Precautions (5.7)*].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications. [see *Warnings and Precautions (5.10)*, *Drug Interactions (7)*].

MAOI Interaction

Inform patients to avoid taking ONSOLIS while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking ONSOLIS [see *Warnings and Precautions (5.1, 5.10)*; *Drug Interactions (7)*].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions (5.11)*].

Important Administration Instructions [see *Dosage and Administration (2)*]

- Instruct patients not to take ONSOLIS for acute pain, postoperative pain, pain from injuries, headache, migraine, or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Inform patients on the meaning of opioid tolerance and ONSOLIS is only to be used as a supplemental pain medication for patients with pain requiring regular opioids, who have developed tolerance to the opioid medication and who need additional opioid treatment of breakthrough pain episodes.
- Advise patients that if they are not taking an opioid medication on a regular around-the-clock basis, they must not take ONSOLIS.

- Advise patients that ONSOLIS contains fentanyl, which is a pain medication similar to hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol.
- Instruct patients that they must wait at least 2 hours before treating a new episode of breakthrough pain with ONSOLIS.
- Instruct patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking ONSOLIS and to use ONSOLIS exactly as prescribed by their doctor and not to take ONSOLIS more often than prescribed. *[see Dosage and Administration (2.4)]*
- Instruct patients NOT to share ONSOLIS and that sharing ONSOLIS with anyone else could result in the other individual's death due to overdose.
- Instruct patients to use ONSOLIS exactly as prescribed by their doctor and not to take ONSOLIS more often than prescribed.
- Provide patients and their caregivers with a Medication Guide each time SUBSYS is dispensed because new information may be available.

Hypotension

Inform patients that ONSOLIS may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.12)]*.

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in ONSOLIS. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform patients that prolonged use of ONSOLIS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that ONSOLIS may cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1), Nonclinical Toxicology 13.1]*.

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that ONSOLIS may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will

react to the medication [see *Warnings and Precautions (5.16)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see *Adverse Reactions (6)*, *Clinical Pharmacology (12.2)*].

Disposal of Unused ONSOLIS

- Advise patients and their household members to dispose of any unneeded films remaining from a prescription as soon as they are no longer needed.
- To dispose of the unneeded ONSOLIS films:
 1. Remove the ONSOLIS film from its foil package.
 2. Drop the ONSOLIS film into the toilet.
 3. Repeat steps 1 and 2 for each ONSOLIS film. Flush the toilet after all unneeded films have been put into the toilet.
- Do not flush the ONSOLIS foil packages or cartons down the toilet [see *How Supplied (16)* and *Storage and Handling (16)*].
- Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of Onsolis are provided in the Medication Guide. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.
- In the event that a caregiver requires additional assistance in disposing of excess unneeded films that remain in the home after a patient has expired, instruct them to call BioDelivery Sciences International, Inc. at 1-877-579-4578 or seek assistance from their local Drug Enforcement Agency (DEA) office.

[Sponsor: Insert manufacturer, packer, or distributor] Company Name
Address line 1 Address line 2 City, State, and Zip Code

Manufactured for and Distributed by:

Company Name
Address line 1, Address line 2, City, State (abbrev.) Zip

IN-500012-03

Rev. 12/2016

Medication Guide

ONSOLIS (fon sol is)

(fentanyl buccal soluble film) , C

IMPORTANT:

Do not use ONSOLIS unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep ONSOLIS in a safe place away from children.

Get emergency medical help right away if:

- a child takes ONSOLIS. ONSOLIS can cause an overdose and death in any child who takes it.
- an adult who has not been prescribed ONSOLIS uses it.
- an adult who is not already taking opioids around-the-clock, uses ONSOLIS.

These are medical emergencies that can cause death. If possible, try to remove ONSOLIS from the mouth.

ONSOLIS is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage breakthrough pain in adults (18 years of age and older) with cancer, who are already routinely taking other opioid pain medicines around-the-clock for cancer pain. ONSOLIS is started only after you have been taking other opioid pain medicines and your body has become used to them(you are opioid tolerant). Do not use ONSOLIS if you are not opioid tolerant.
- A medicine that contains fentanyl in a small film (about the size of a dime or nickel) that sticks to the inside of your cheek.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about ONSOLIS:

- **Get emergency help right away if you take too much ONSOLIS (overdose).** When you first start taking ONSOLIS, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- **Taking ONSOLIS with other opioid medicines**, that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs **can cause severe drowsiness, confusion, breathing problems, coma, and death.**
- Never give anyone else your ONSOLIS. They could die from taking it. Store ONSOLIS away from children and in a safe place to prevent stealing or abuse. Selling or giving away ONSOLIS is against the law.

- If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using ONSOLIS. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
- ONSOLIS is available only through a program called the **Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program**. To receive ONSOLIS, you must
 - talk to your healthcare provider
 - understand the benefits and risks of ONSOLIS
 - agree to all the instructions
 - sign the Patient-Prescriber Agreement form.
- ONSOLIS is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you have your ONSOLIS prescription filled.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.
- Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Do not take ONSOLIS if:

- You are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- You are allergic to any of the ingredients in ONSOLIS. See the end of this Medication Guide for a complete list of ingredients in ONSOLIS.
- You have short-term pain that you would expect to go away in a few days, such as

- pain after surgery
- headache or migraine
- dental pain

**Before taking ONSOLIS, tell your healthcare provider if you have a history of:
troubled breathing or lung problems such as asthma, wheezing or shortness of breath**

- head **injury, seizures**
- problems urinating
- slow heart **rate** or other heart problems
- low blood **pressure**
- abuse of street or prescription drugs alcohol addiction, or Mental health problems]
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of ONSOLIS during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** ONSOLIS passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ONSOLIS with certain other medicines can cause serious side effects that could lead to death.

When taking ONSOLIS:

- Do not change your dose. Take ONSOLIS exactly as prescribed by your healthcare provider.
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use ONSOLIS.**
- See the Instructions for Use below for information about how to take ONSOLIS. Do not chew or swallow ONSOLIS,
- **You must not take a dose of ONSOLIS more than 1 time for each episode of breakthrough cancer pain.**
- You must wait at least **2** hours between doses before treating a new episode of breakthrough cancer pain with ONSOLIS.
- Talk to your healthcare provider if your dose of ONSOLIS does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of ONSOLIS needs to be changed.
- You must not use ONSOLIS for more than four episodes of breakthrough cancer pain in one day. Talk to your healthcare provider if you have more than four episodes of breakthrough pain each day. The dose of the around-the-clock opioid pain medicine for your constant pain may need to be changed.
- If you use too much ONSOLIS or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.
- Dispose of any unopened ONSOLIS films as soon as you no longer need them:
 - Remove the ONSOLIS film from its foil package.
 - Drop the ONSOLIS film into the toilet.
 - Repeat steps 1 and 2 for each ONSOLIS film. Flush the toilet after all unneeded films have been put into the toilet.
 - Do not flush the ONSOLIS foil packages or cartons down the toilet.
 - If you need help with disposal of ONSOLIS, call BioDelivery Sciences International, Inc. at 1-877-579-4578 or call your local Drug Enforcement Agency (DEA) office/
- If you have been taking ONSOLIS regularly, do not stop taking ONSOLIS without talking to your healthcare provider.

- **DO NOT** Drive or operate heavy machinery, until you know how ONSOLIS affects you. ONSOLIS can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ONSOLIS may cause you to overdose and die.
- **DO NOT** switch from ONSOLIS to other medicines that contain fentanyl without talking to your healthcare provider. The amount of fentanyl in a dose of ONSOLIS is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of ONSOLIS that may be different than other fentanyl containing medicines you may have been taking.

The possible side effects of ONSOLIS:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, weakness, anxiety, depression, rash, trouble sleeping, low red blood cell count, swelling of the arms, hands, legs and feet. Call your healthcare provider if you have any of these symptoms and they are severe.
- .
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, (*for oxymorphone add* or hands, hives, itching, rash,) extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have used too much ONSOLIS or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more ONSOLIS until you have talked to your healthcare provider.**

These are not all the possible side effects of ONSOLIS. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

What are the ingredients in ONSOLIS

Active ingredient: fentanyl citrate

Inactive ingredients: carboxymethylcellulose, citric acid, hydroxyethyl cellulose, hydroxypropyl cellulose, methylparaben, monobasic sodium phosphate, peppermint oil, polycarbophil, propylene glycol, propylparaben, sodium benzoate, sodium hydroxide, sodium saccharin, titanium dioxide, tribasic sodium phosphate, vitamin E acetate, and water.

Patient Instructions for Use

Before you use ONSOLIS, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use ONSOLIS the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use ONSOLIS.

ONSOLIS comes in a foil package. **Do not open the package until ready to use.** Once opened, use the entire ONSOLIS film right away.

To open an ONSOLIS package:

1. With the back side of the foil package facing you, cut along arrows with scissors. (See figure A)
2. Repeat step above to open the other side of the package.
3. Separate the layers of the foil package and remove the ONSOLIS film. (See figure B)

Figure A

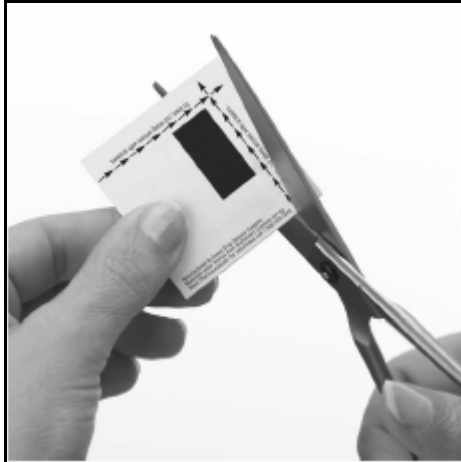
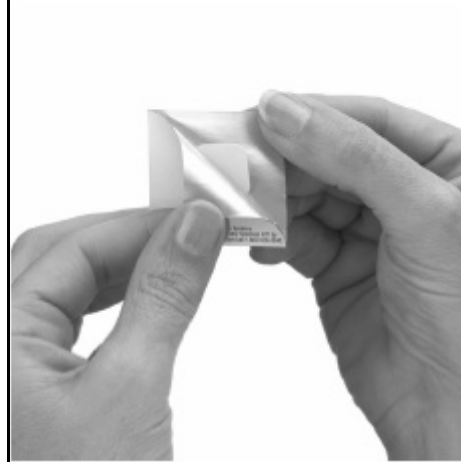


Figure B



- **Do not chew or swallow ONSOLIS.** If you do, you will likely get less relief for your breakthrough cancer pain.
- **Do not cut or tear the ONSOLIS film.**
- To correctly use ONSOLIS (see figures below):
- Use your tongue to wet the inside of your cheek or, if needed, rinse your mouth with water to wet the area in your mouth where you will place ONSOLIS.
- Hold the ONSOLIS film in place on a clean, dry finger with the printed side facing up. (See figure C)
- Carefully **place** the ONSOLIS film inside your mouth with the printed side against the inside of your

moistened cheek. (See figure D)

- With your finger, **press** the ONSOLIS film against your cheek. Hold it there for 5 seconds.
- Take your finger away from the ONSOLIS film. It will stick to the inside of your cheek.
- Leave the film in place until it dissolves, usually within 15 to 30 minutes after you apply it.
- You may drink liquids after 5 minutes.
- If your healthcare provider tells you to use more than one ONSOLIS film at the same time for your breakthrough cancer pain, do not put the films on top of each other. ONSOLIS films may be placed on either side of your mouth.
- Avoid touching or moving the film while it dissolves.
- Do not eat any food until after the film dissolves.

Figure C



Figure D



If you can not use ONSOLIS this way, talk with your healthcare provider about other choices to treat your breakthrough cancer pain.

Manufactured by: [Insert name and address] and/or Distributed by: [Insert name and address], www.ITRADENAMEI.com or call 1-800-XXX-XXXX

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: month/year