ONSOLIS™

(fentanyl buccal soluble film)

C II

IN-500012-01 Rev. 7/09

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

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

See full prescribing information for complete boxed warning.

- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **Must only be used in opioid tolerant patients. (1)**
- **Life-threatening respiratory depression could occur in patients not taking chronic opiates. (5.1)**
- **Contraindicated in management of acute or postoperative pain. (4)**
- **Do not substitute for any other fentanyl products. (5.3)**
- **Contains fentanyl in an amount that can be fatal to a child. Keep out of reach of children and dispose of unneeded films properly. (5.2)**
- **Use with CYP3A4 inhibitors may cause potentially fatal respiratory depression. (7)**
- ONSOLIS is available only through a restricted distribution program called the FOCUS Program and requires prescriber, pharmacy, and patient enrollment. (5.3.1)

INDICATIONS AND USAGE

ONSOLIS is an opioid analgesic indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, **who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** (1)

DOSAGE AND ADMINISTRATION

- Initial starting dose of 200 mcg ONSOLIS in all patients. (2.1)
- 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. (2.1)
- Maximum is one dose per episode; no more than four doses per day; separate by at least 2 hours. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

- Buccal soluble film in 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1200 mcg dosage strengths. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. (4)
- Intolerance or hypersensitivity to fentanyl, ONSOLIS, or its components. (4)

WARNINGS AND PRECAUTIONS

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1, 5.4)
- ONSOLIS films contain medicine that can be fatal to a child. Ensure proper storage and disposal. (5.2, 16.2)
- Use with other CNS depressants or CYP3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4, 7)
- ONSOLIS may impair ability for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). (5.5)
- Titrate ONSOLIS cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to hypoventilation. (5.6)
- Administer ONSOLIS with extreme caution in patients susceptible to intracranial effects of CO_2 retention. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (frequency ≥10%): 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

- Monitor patients who begin therapy with, or increase the dose of, inhibitors of CYP3A4 for signs of opioid toxicity. (5.4, 7)
- Monitor patients who stop therapy with, or decrease the dose of, inducers of CYP3A4 for signs of opioid toxicity. (7)

USE IN SPECIFIC POPULATIONS

- Safety and efficacy below age 18 years have not been established. (8.4)
- Administer ONSOLIS with caution to patients with renal or hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. **Revised: July 2009**

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

ONSOLIS contains fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics. This should be considered when prescribing or dispensing ONSOLIS in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances, which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ONSOLIS for any other fentanyl product may result in fatal overdose.

ONSOLIS is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ONSOLIS is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis.

ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS. Patients beginning treatment with ONSOLIS must begin with titration from the 200 mcg dose [see *Dosage and Administration* (2)].

When dispensing, do not substitute an ONSOLIS prescription for any other fentanyl product. 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. As a result of these differences, the substitution of ONSOLIS for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ONSOLIS. If the breakthrough pain episode is not relieved, patients should wait at least 2 hours before taking another dose [see *Dosage and Administration* (2)].

ONSOLIS is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that ONSOLIS contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All ONSOLIS films must be kept out of the reach of children [see *Patient Counseling Information* (17)].

The concomitant use of ONSOLIS with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations and may cause potentially fatal respiratory depression [see *Drug Interactions* (7)].

Because of the risk for misuse, abuse, and overdose, ONSOLIS is available only through a restricted distribution program, called the FOCUS Program. Under the FOCUS Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive ONSOLIS. To enroll in the FOCUS Program, call 1-877-466-7654 (1-877-4ONSOLIS) or visit www.OnsolisFocus.com [see *Warnings and Precautions* (5.3.1)].

1 INDICATIONS AND USAGE

ONSOLIS (fentanyl buccal soluble film) is an opioid analgesic indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, **who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression could occur in patients not taking chronic opiates. For this reason, ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

ONSOLIS is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

2 DOSAGE AND ADMINISTRATION

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

Only prescribers enrolled in the FOCUS Program may prescribe ONSOLIS [see *Warnings and Precautions* (5.3.1)].

2.1 Dose Titration

The goal of dose titration is to find 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.

Starting Dose: 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. Due to differences in pharmacokinetic properties and individual variability, **patients switching from another oral transmucosal fentanyl product must be started on no greater than 200 mcg of ONSOLIS. When prescribing, do not switch patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS** as ONSOLIS is not equivalent on a mcg per mcg basis with any other fentanyl product. ONSOLIS is NOT a generic version of any other oral transmucosal fentanyl product.

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

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 the 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 and 800 mcg ONSOLIS, the patient should use or safely dispose of all remaining 200 mcg ONSOLIS films [see *Disposal of ONSOLIS (*16.2)]. Patients who require 1200 mcg ONSOLIS, should dispose of all remaining unused 200 mcg ONSOLIS films [see *Disposal of ONSOLIS* (16.2)]. 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 is available in five dosage strengths:
200, 400, 600, 800, and **1200 mcg**

The initial dose is 200 mcg ONSOLIS

Titrate by incrementally increasing the dose once per episode

Fentanyl dose	200 mcg	400 mcg	600 mcg	800 mcg	1200 mcg
Using	200 mcg ONSOLIS film(s)				1200 mcg ONSOLIS film
Number of films	1	2	3	4	1

If adequate pain relief *is achieved*, treat subsequent breakthrough cancer pain episodes using the determined dose.

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.

2.2 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 (2.1). 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.

2.3 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 pink side facing up and hold in place. Place the pink 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 has dissolved.

3 DOSAGE FORMS AND STRENGTHS

ONSOLIS is a buccal soluble film with a white side and a pink side. The pink side contains a bioadhesive polymer and the active ingredient. Each strength is marked on the white side of the film with an identifying number. ONSOLIS is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1200 mcg strengths [see *How Supplied* (16.3) and *Storage and Handling* (16.1)].

4 CONTRAINDICATIONS

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer.

ONSOLIS is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products.

5 WARNINGS AND PRECAUTIONS

See *Boxed Warning* - WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

5.1 Respiratory Depression (Hypoventilation)

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in ONSOLIS. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.2 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that ONSOLIS contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. Patients and their caregivers must be instructed to keep ONSOLIS out of the reach of children. [see *How Supplied* (16.3), *Storage and Handling* (16.1), and *Patient Counseling Information* (17)].

Physicians 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.

5.3 ONSOLIS Dispensing

When dispensing, do not substitute an ONSOLIS prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of ONSOLIS compared to other fentanyl products (e.g., see Figure 1) that result in clinically important differences in the extent of absorption of fentanyl. **As a result of these differences, the substitution of ONSOLIS for any other fentanyl product may result in fatal overdose. ONSOLIS is NOT a generic version of any other transmucosal fentanyl product.**

5.3.1 ONSOLIS Distribution Program

ONSOLIS is available only through a restricted distribution program called the FOCUS Program. Under the FOCUS Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive ONSOLIS. This program provides educational materials, patient counseling and facilitated distribution of the drug. To enroll in the FOCUS Program, call 1-877-466-7654 (1-877-4ONSOLIS) or visit www.OnsolisFocus.com. Prescribers and patients are required to understand the risks of therapy with ONSOLIS. Prescribers are required to understand the information in the prescribing information and to:

- **Ensure proper patient selection, including that the patient is opioid tolerant**
- **Educate patients about the benefits and risks of treatment with ONSOLIS and ensure that the patient receives the Medication Guide**
- **Complete the FOCUS Program prescriber enrollment form; sign and fax the form to the FOCUS Program**
- **Obtain the patient's signature on the patient enrollment form; sign and fax the form to the FOCUS Program**
- **Follow FOCUS Program-specific procedures for prescribing ONSOLIS using a courier**

5.4 Additive CNS Depressant Effects

The concomitant use of ONSOLIS with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., hypoventilation, hypotension, and profound sedation). Concomitant use with inhibitors of the cytochrome P450 3A4 (CYP3A4) isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [see *Drug Interactions* (7)].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of ONSOLIS if warranted.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking ONSOLIS of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate ONSOLIS with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation. In such patients, even normal therapeutic doses of ONSOLIS may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer ONSOLIS with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.8 Cardiac Disease

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

5.9 MAO Inhibitors

ONSOLIS is not recommended for use in patients who have received MAO inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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 adverse reactions seen with ONSOLIS are typical opioid side effects in a population with cancer. Frequently, opioid-associated adverse reactions will cease or decrease in intensity with continued use of ONSOLIS. Expect opioid side effects and manage them accordingly.

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.

Because clinical trials are conducted under widely varying conditions, adverse event 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.

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 ≥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 ≥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 ≥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

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when ONSOLIS is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of ONSOLIS with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving ONSOLIS who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done conservatively [see *Warnings and Precautions* (5.4)].

The concomitant use of ONSOLIS with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of ONSOLIS. Patients receiving ONSOLIS who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased ONSOLIS activity and the dose of ONSOLIS should be adjusted accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women.

ONSOLIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

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.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for ONSOLIS.

Fentanyl citrate was not teratogenic when administered to pregnant animals. In published studies, pregnant rats were treated with fentanyl (10, 100, or 500 mcg/kg/day) via implanted microosmotic minipumps from Day 7 to 21 of their 21 day gestation period. Fentanyl was not teratogenic at doses up to 500 mcg/kg/day [approximately 3 times the maximum recommended human dose (MRHD) of 1200 mcg for ONSOLIS per breakthrough cancer pain episode]. Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation Day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, use of ONSOLIS during labor and delivery is not recommended.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, ONSOLIS should not be used in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using ONSOLIS.

8.4 Pediatric Use

Safety and efficacy in 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 of ONSOLIS, 98 (32.0%) were 65 years of age and 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 population. Therefore, exercise caution when individually titrating ONSOLIS in elderly patients to provide adequate efficacy while minimizing risk.

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.

8.7 Gender

Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse reactions.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. ONSOLIS may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Manage the handling of ONSOLIS to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [see *How Supplied* (16.3) and *Storage and Handling* (16.1)].

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians 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 addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since ONSOLIS may be abused for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse of this product.

9.3 Dependence

Guide the administration of ONSOLIS by the response of the patient.

Physical dependence is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug.

Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of ONSOLIS overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation [see *Clinical Pharmacology – Pharmacodynamics* (12.2)].

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the ONSOLIS film, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and employ naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

10.4 Treatment of Overdose in Opioid Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

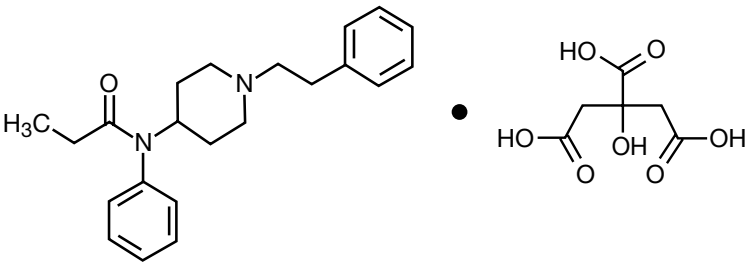
Management of severe ONSOLIS overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

Although muscle rigidity interfering with respiration has not been seen following the use of ONSOLIS, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by the administration of an opioid antagonist, and, as a final alternative, by the administration of a neuromuscular blocking agent.

11 DESCRIPTION

ONSOLIS (fentanyl buccal soluble film) is an oral transmucosal form of the potent opioid analgesic, fentanyl citrate, intended for application to the buccal mucosa. ONSOLIS uses the BioErodible MucoAdhesive (BEMA™) bilayer delivery technology which is comprised of water-soluble polymeric films. ONSOLIS consists of a pink bioadhesive layer bonded onto a white inactive layer. 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.

Active Ingredient: Fentanyl citrate, USP is *N*-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1). Fentanyl 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 molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. Fentanyl citrate has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Conditions which decrease fentanyl clearance including hepatic dysfunction and co-administration of CYP3A4 inhibitors may lead to increased duration of exposure. However, the duration of effect for the initial dose of fentanyl is largely determined by the rate of distribution of the drug. Diminished metabolic clearance may become significant with repeated dosing or at very high single doses.

Analgesia

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. As a result, the dose of ONSOLIS should be individually titrated to achieve the desired effect [see *Dosage and Administration* (2)].

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu*-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to 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 origin may produce similar findings).

Gastrointestinal System

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

Cardiovascular System

Fentanyl may produce a release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone in humans. They also stimulate prolactin secretion, growth hormone secretion, and pancreatic secretion of insulin and glucagon in humans and other species, e.g., rats and dogs. Thyroid stimulating hormone has been shown to be both inhibited and stimulated by opioids.

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. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of ONSOLIS. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication [see *Boxed Warning - Warnings: Importance of Proper Patient Selection and Potential for Abuse, Contraindications* (4), *Warnings and Precautions* (5), *Adverse Reactions* (6), and *Overdosage* (10)].

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.

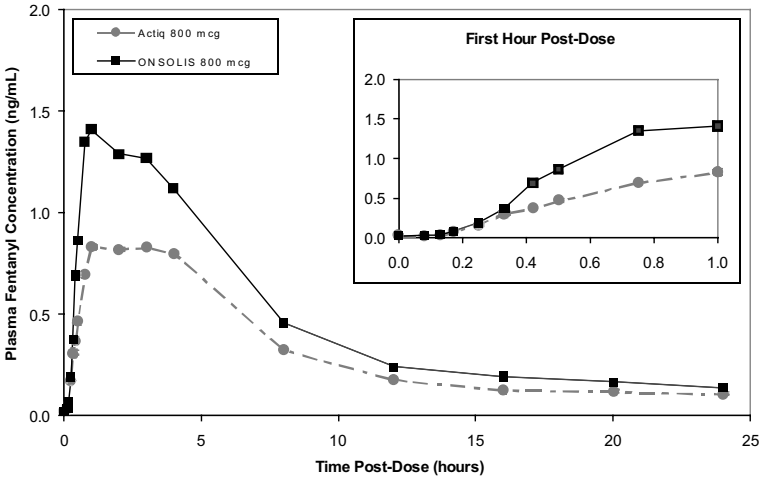
In a study that compared the relative bioavailability of ONSOLIS and Actiq* (oral transmucosal fentanyl citrate [OTFC]) in 12 adult normal volunteers, the rate and extent of fentanyl absorption were considerably greater with ONSOLIS [62% greater maximum plasma concentration (C_{max}) and 40% greater systemic exposure (AUC_{inf})] (Table 3 and Figure 1).

Table 3
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 4. 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 4
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 5. 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 5
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.

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)].

Elimination

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

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

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.

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.

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.

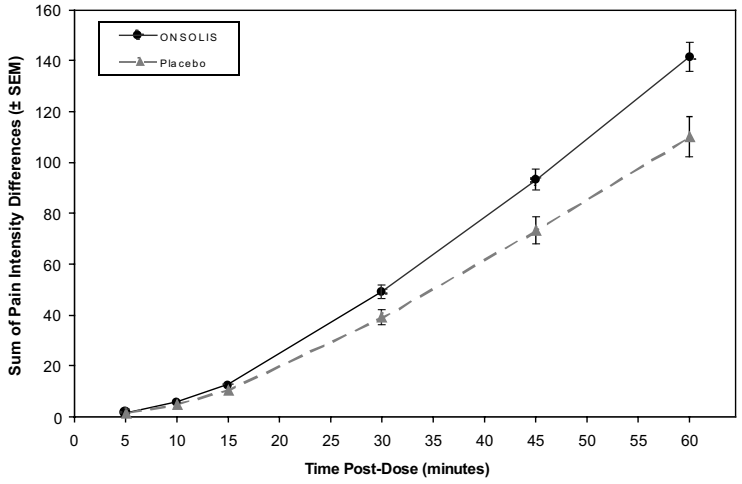
A double-blind, placebo-controlled, crossover study was performed in patients with cancer to evaluate the effectiveness of ONSOLIS for the treatment of breakthrough cancer pain. Open-label titration identified a successful dose of ONSOLIS, within the range of 200 to 1200 mcg. A "successful" dose was 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 6
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 Placeboin Adult Patients with Breakthrough Cancer Pain



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

ONSOLIS is supplied in individually-sealed child-resistant foil packages. The amount of fentanyl contained in ONSOLIS can be fatal to a child. The entire ONSOLIS film should be used immediately after opening the child-resistant package. Patients and their caregivers must be instructed to keep ONSOLIS out of the reach of children [see *Boxed Warning - Warnings: Importance of Proper Patient Selection and Potential For Abuse, Warnings And Precautions* (5), and *Patient Counseling Information* (17)].

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.

16.2 Disposal of ONSOLIS

Patients and members of their household must be instructed to dispose of any unneeded films remaining from a prescription as soon as they are no longer needed. The ONSOLIS film should be removed from its foil package and dropped into the toilet. This should be repeated 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.

Instructions for disposal are also included in *Disposal of Unneeded ONSOLIS Films* (17.2) and in the *Medication Guide* (17.3).

If additional assistance is required, call Meda Pharmaceuticals Inc. at 1-800-526-3840.

16.3 How Supplied

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 pink side. The white side is debossed with an identifying number. The dosage strength of each film is indicated by the code on the white 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)	Deboss Code(s)	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.**

17 PATIENT COUNSELING INFORMATION

See *Medication Guide* (17.3) for specific patient instructions.

17.1 Patient/Caregiver Instructions

Patients will need to be enrolled in the FOCUS Program to receive ONSOLIS. The patient will receive their prescription via a traceable courier (with proof of delivery and adult signature required). The patient will receive a counseling call at the time of the first prescription to verify that they are opioid tolerant and discuss how to use the drug.

Provide patients and their caregivers with a Medication Guide for ONSOLIS (17.3).

Patients and their caregivers must be instructed that ONSOLIS contains medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. Patients and their caregivers must be instructed to keep ONSOLIS out of the reach of children. Patients and members of their household must be instructed to dispose of any unneeded films remaining from a prescription as soon as possible [see *How Supplied* (16.3) and *Storage and Handling* (16.1)].

Physicians 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.

17.2 Disposal of Unneeded ONSOLIS Films

Patients and members of their household must be instructed on the safe disposal 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* (16.3) and *Storage and Handling* (16.1)].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of ONSOLIS are provided in the Medication Guide (17.3). 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 Meda Pharmaceuticals Inc. at 1-800-526-3840 or seek assistance from their local Drug Enforcement Agency (DEA) office.

17.3 Medication Guide

ONSOLIS™ (än-sŏ'-lĭs) **CII**
(fentanyl buccal soluble film)

200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg

IMPORTANT:
Do not use ONSOLIS unless you are regularly using another opioid pain medicine around-the-clock for your constant cancer pain and your body is used to this medicine (opioid tolerant).
Keep ONSOLIS in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. Get emergency help right away if a child takes ONSOLIS by accident. If possible, try to remove ONSOLIS from the child's mouth.

Read this Medication Guide before you start using ONSOLIS and each time you get a new prescription. There may be new information. Share this important information with members of your household. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about ONSOLIS?

1. **ONSOLIS can cause life-threatening breathing problems which can lead to death, if:**
   - you are not regularly using another opioid pain medicine around-the-clock for your constant cancer pain and your body is not used to this medicine. This means that you are not opioid tolerant;
   - you do not use ONSOLIS exactly as prescribed by your doctor; or
   - a child takes ONSOLIS by accident.

   See the section "What are the possible side effects of ONSOLIS?" for more information about side effects.
2. **ONSOLIS contains the pain medicine fentanyl.** Your doctor may prescribe a starting dose that is different from other fentanyl-containing medicines. Do not substitute ONSOLIS for other fentanyl medicines, including Actiq* (also called oral transmucosal fentanyl citrate) or Fentora*.
3. **ONSOLIS is available only through the FOCUS Program.** To receive ONSOLIS, you must:
   - talk to your doctor
   - understand the benefits and risks of ONSOLIS
   - agree to all of the instructions
   - register in the FOCUS Program

What is ONSOLIS?

ONSOLIS is a prescription medicine that contains fentanyl. ONSOLIS is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be abused by people who abuse prescription medicines or street drugs.

ONSOLIS contains fentanyl in a small film (about the size of a dime or nickel) that sticks to the inside of your cheek.

ONSOLIS is used to treat breakthrough pain in adults with cancer (18 years of age and older) who regularly use another opioid pain medicine around-the-clock for their constant cancer pain. ONSOLIS is started only after you have been taking another opioid pain medicine and your body is used to it (you are opioid tolerant). **Do not use ONSOLIS if you are not opioid tolerant.**

- You must stay under your doctor's care while taking ONSOLIS.
- **Prevent theft, misuse or abuse. Keep ONSOLIS in a safe place** to protect it from being stolen. ONSOLIS can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Never give ONSOLIS to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.
- **Selling or giving away this medicine is against the law.**
- **It is not known if ONSOLIS is safe and effective in children under the age of 18 years.**

ONSOLIS is only given to people who are:

- enrolled in the FOCUS Program
- opioid tolerant

Who should not use ONSOLIS?

Do Not Use ONSOLIS if you:

- Are not already taking another opioid pain medicine around-the-clock for your constant cancer pain
- Only have pain for a short time, pain from surgery, headache, migraine, or dental pain
- Are allergic to any of the ingredients in ONSOLIS. See the end of this Medication Guide for a complete list of ingredients in ONSOLIS.

What should I tell my doctor before starting ONSOLIS?

Tell your doctor about all of your medical and mental health problems, especially if you have:

- trouble breathing or lung problems such as asthma, wheezing or being short of breath
- a head injury or brain problem
- liver or kidney problems
- seizures (convulsions or fits)
- slow heart rate or other heart problems
- low blood pressure
- mental health problems such as major depression or hallucinations (seeing or hearing things that are not real)
- past or present drinking problem or alcoholism for you or a family member
- past or present drug abuse or addiction problems for you or a family member

Tell your doctor if you are:

- **Pregnant or planning to become pregnant.** ONSOLIS may harm your unborn baby.
- **Breast feeding.** ONSOLIS passes through your breast milk. It can cause serious harm to your baby. You should not use ONSOLIS while breast feeding.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with ONSOLIS. Sometimes the doses of certain medicines and ONSOLIS may need to be changed if used together.

- Do not take any medicine while using ONSOLIS until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using ONSOLIS.
- Be very careful about taking other medicines that make you sleepy, such as other pain medicines or some depression medicines (antidepressants that make you sleepy), sleeping pills, anxiety medicines, tranquilizer medicines, or some allergy medicines (antihistamines that make you sleepy).

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

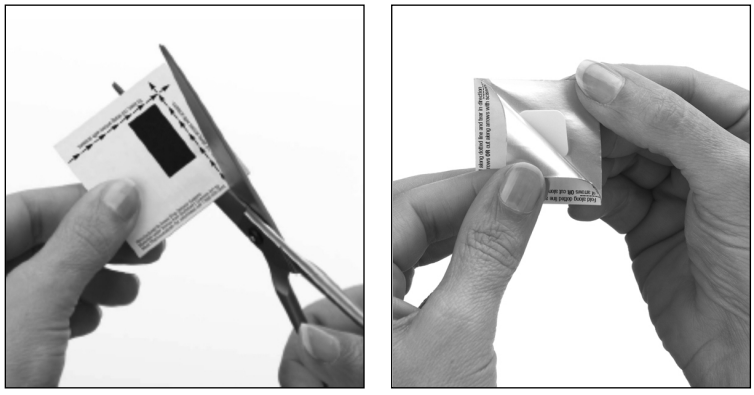
How should I use ONSOLIS?

- Before you can begin to receive ONSOLIS:
  - your doctor will explain the FOCUS Program to you
  - you will sign the FOCUS Patient Enrollment Form
  - you will receive counseling from the FOCUS Program call center
  - for more information about the FOCUS Program, go to www.OnsolisFocus.com or call 1-877-466-7654 (1-877-4ONSOLIS)
- ONSOLIS will be delivered directly to you from a special pharmacy.
- Use ONSOLIS exactly as prescribed by your doctor. Do not use ONSOLIS more often than prescribed.
  - Your doctor will change the dose until you and your doctor find the right dose for you.
  - ONSOLIS should be used only one time for each episode of breakthrough cancer pain. Separate doses of ONSOLIS by at least 2 hours.
  - Do not use ONSOLIS for more than four episodes of breakthrough cancer pain in one day. Talk to your doctor if you have more than four episodes of breakthrough pain each day. The dose of the opioid pain medicine for your constant pain may need to be changed.
  - Once the right dose for you has been found, do not change your dose of ONSOLIS yourself.
- Talk to your doctor if your dose of ONSOLIS does not relieve your breakthrough cancer pain. Your doctor will decide if your dose of ONSOLIS needs to be changed.
- 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 (as shown in Medication Guide Figure A below):

1. With the back side of the foil package facing you, cut along arrows with scissors.
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.

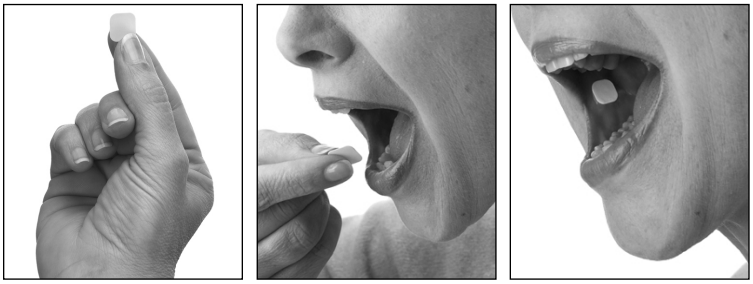
Medication Guide Figure A
Opening an ONSOLIS Foil Package



- **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 (as shown in Medication Guide Figure B 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 **pink** side facing up.
  - Carefully **place** the ONSOLIS film inside your mouth with the pink side against the inside of your moistened cheek.

- 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 doctor 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.

Medication Guide Figure B
Correct Administration of ONSOLIS



- If you can not take ONSOLIS this way, talk with your doctor about other choices to treat your breakthrough cancer pain.
- If you take too much ONSOLIS, you, your caregiver, or someone else nearby should call 911 for emergency help.

What should I avoid while taking ONSOLIS?

- **Do not drive, operate machinery, or do other dangerous activities** until you know how ONSOLIS affects you. ONSOLIS can make you sleepy. Ask your doctor when it is okay to do these activities.
- **Do not drink alcohol while using ONSOLIS.** It can increase your chance of having dangerous side effects.
- **Do not take any medicine while using ONSOLIS until you have talked with your doctor.** Your doctor will tell you if you can take other medicines while you are using ONSOLIS.
- **Be very careful about taking other medicines that make you sleepy** such as other pain medicines or some depression medicines (antidepressants that make you sleepy), sleeping pills, anxiety medicines, tranquilizer medicines, or some allergy medicines (antihistamines that make you sleepy).

What are the possible side effects of ONSOLIS?

You or a family member should call your doctor or get emergency medical help right away if you have any of the symptoms below:

- trouble breathing
- drowsiness with slow breathing
- slow, shallow breathing (little chest movement with breathing)
- feel faint, dizzy, confused, or have other unusual symptoms

These can be symptoms of an overdose of ONSOLIS. Your dose of ONSOLIS may be too high for you. **These symptoms may lead to serious problems or death if not treated right away. Do not take another dose of ONSOLIS.**

- **ONSOLIS can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.
- **ONSOLIS can cause physical dependence.** Do not stop taking ONSOLIS or any other opioid without talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
- **There is a chance of abuse or addiction with ONSOLIS.** The chance is higher if you have ever been addicted to or abused other medicines, street drugs, or alcohol, or have a history of mental health problems.

The most common side effects of ONSOLIS are:

- nausea
- vomiting
- dizziness
- loss of too much body fluid (dehydration)
- shortness of breath
- sleepiness

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including ONSOLIS and is unlikely to go away without treatment. Talk to your doctor about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking ONSOLIS.

Talk with your doctor about any side effects that bother you or do not go away. These are not all the side effects of ONSOLIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ONSOLIS?

- **Always keep ONSOLIS in a safe place away from children and from anyone for whom it has not been prescribed.** Protect it from theft.
- Store ONSOLIS at room temperature, 59° to 86°F (15° to 30°C) until ready to use.
- Do not freeze ONSOLIS.
- Keep ONSOLIS from getting wet (protect from moisture).

How should I dispose of unopened ONSOLIS films when they are no longer needed?

- Dispose of unopened ONSOLIS films as soon as you no longer need them:
  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.
- If you need help with disposal of ONSOLIS, call Meda Pharmaceuticals Inc. at 1-800-526-3840 or call your local Drug Enforcement Agency (DEA) office.

General information about the safe and effective use of ONSOLIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use ONSOLIS only for the purpose for which it was prescribed. Do not give ONSOLIS to other people, even if they have the same symptoms you have.

ONSOLIS can harm other people and can even cause death.

Sharing ONSOLIS is against the law.

This Medication Guide summarizes the most important information about ONSOLIS. For more information talk with your doctor or pharmacist. You can ask your pharmacist or doctor for information about ONSOLIS that is written for healthcare professionals. For more information about ONSOLIS go to www.Onsolis.com or call Meda Pharmaceuticals Inc. at 1-800-526-3840.

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, red iron oxide, sodium benzoate, sodium hydroxide, sodium saccharin, titanium dioxide, tribasic sodium phosphate, vitamin E acetate, and water.

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Marketed under license from BioDelivery Sciences International Inc., Raleigh, North Carolina, 27607 USA by Meda Pharmaceuticals Inc., Somerset, New Jersey, 08873 USA

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U.S. Patents 5,800,832; 6,159,498

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