HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUBSYS safely and effectively. See full prescribing information for SUBSYS.
SUBSYS™ (fentanyl sublingual spray), CII
Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL
See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depression, SUBSYS is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4)**
- **Keep out of reach of children. (5.3)**
- **Use with CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to SUBSYS. (5.1)**
- **When dispensing, do not substitute with any other fentanyl products. (5.1)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **SUBSYS 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. (5.10)**

----------INDICATIONS AND USAGE----------
SUBSYS 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 opioid therapy for their underlying persistent cancer pain. Patients must remain on around-the-clock opioids when taking SUBSYS. (1)
Limitations of Use:
SUBSYS may be dispensed only to patients enrolled in the TIRF REMS ACCESS program.

----------DOSAGE AND ADMINISTRATION----------
- Patients must require and use around-the-clock opioids when taking SUBSYS. (1)
- Initial dose of SUBSYS: 100 mcg.
- Individually titrate to a tolerable dose that provides adequate analgesia using a single SUBSYS dose per breakthrough cancer pain episode. (2)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS. (2.3)
- Limit consumption to four or fewer doses per day once successful dose is found. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Sublingual spray in 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg dosage strengths. (3)

----------CONTRAINDICATIONS----------
- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraine and dental pain (4)
- Intolerance or hypersensitivity to fentanyl, SUBSYS, or its components. (4)

----------WARNINGS AND PRECAUTIONS----------
- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Full and consumed SUBSYS units contain medicine that can be fatal to a child. Ensure proper storage and disposal. (5.3, 16.2)
- Use with other CNS depressants and moderate or strong CYP450 3A4 inhibitors may increase depressant effects including respiratory depression, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate SUBSYS cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO_2 retention. (5.6, 5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions during treatment (frequency ≥5%): vomiting, nausea, constipation, dyspnea, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Insys Therapeutics, Inc., at 1-855-978-2797 or FDA at 1-800-FDA-1088 or *www.fda.gov/ medwatch.*

----------DRUG INTERACTIONS----------
- Boxed Warning and Warnings and Precautions (5.4, 7)

----------USE IN SPECIFIC POPULATIONS----------
- Safety and effectiveness in pediatric patients below 18 years of age have not been established. (8.4)
- Administer SUBSYS with caution to patients with liver or kidney dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

Respiratory Depression

Fatal respiratory depression has occurred in patients treated with transmucosal immediate-release fentanyl products such as SUBSYS, including following use in opioid non-tolerant patients and improper dosing. The substitution of SUBSYS for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, SUBSYS is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients.

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. SUBSYS must be kept out of reach of children. ***[see Patient Counseling Information (17.3) and How Supplied/Storage and Handling (16.1)]***

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

Medication Errors

Substantial differences exist in the pharmacokinetic profile of SUBSYS compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose.

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to SUBSYS. ***[see Dosage and Administration (2.1),Warnings and Precautions (5.2,) and Clinical Pharmacolog y(12.3)]***

- When dispensing, do not substitute a SUBSYS prescription for other fentanyl products.

Abuse Potential

SUBSYS contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. SUBSYS can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing SUBSYS in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, SUBSYS is available only through a restricted program required by the Food and Drug Administration, called a Risk **E**valuation and **M**itigation **S**trategy **(REMS)**. Under the **T**ransmucosal **I**mmediate-**R**elease **F**entanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. *[See Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSaccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

SUBSYS is indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking SUBSYS.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, SUBSYS is contraindicated in the management of acute or postoperative pain.

SUBSYS is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Limitations of Use:
As part of the Transmucosal Immediate-Release Fentanyl (TIRF) REMS ACCESS Program, SUBSYS may be dispensed only to outpatients enrolled in the program. [see *Warnings and Precautions* (5.10)]. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of SUBSYS, patient enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe SUBSYS 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 SUBSYS. [see Warnings and Precautions (5.10)]

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

2.1 Initial Dose

Individually titrate SUBSYS to a dose that provides adequate analgesia and minimizes side effects. The initial dose of SUBSYS to treat episodes of breakthrough cancer pain is **always** 100 mcg. **. When prescribing, do not switch patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to SUBSYS** as SUBSYS is not equivalent on a mcg per mcg basis with any other fentanyl product *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

Prescribe an initial titration supply of 100 mcg SUBSYS units, which limits the number of units in the home during titration.

Avoid prescribing a higher dose until patients have used up all units to prevent confusion and possible overdose.

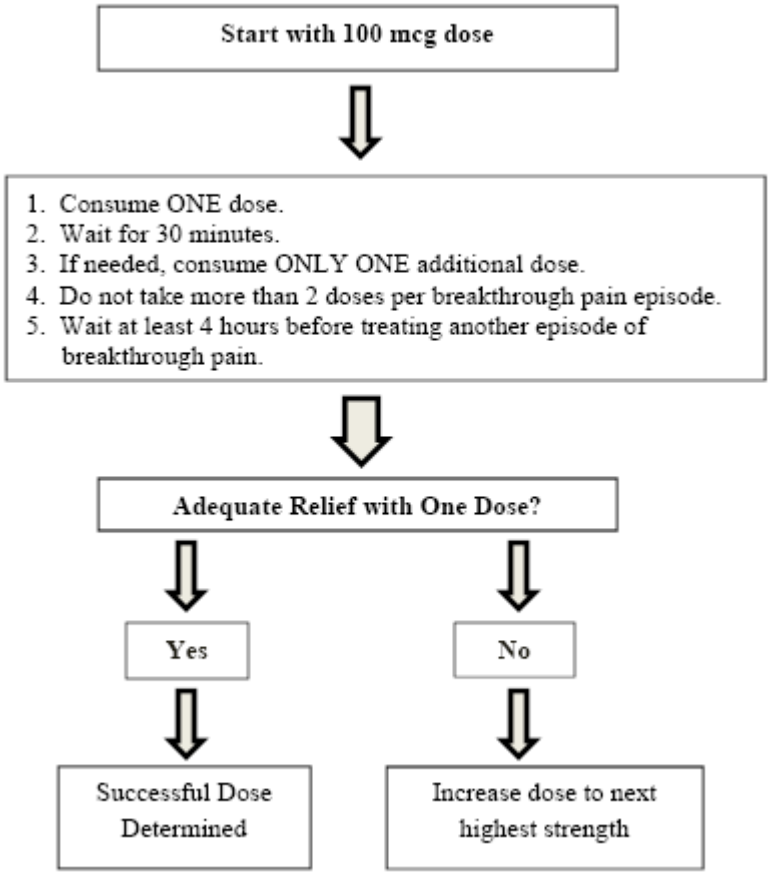
2.2 Dose Titration

a. From the 100 mcg initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single SUBSYS dose per breakthrough cancer pain episode with tolerable side effects. Patients should record their use of SUBSYS over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.
b. For each breakthrough pain episode treated, if pain is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of SUBSYS for any breakthrough pain episode.
c. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with SUBSYS.
d. If there is a need to titrate to a 200 mcg dose, prescribe 200 mcg SUBSYS units.
e. Subsequent titration steps are 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg. See Table 1.
f. To reduce the risk of overdose during titration, patients should have only one strength of SUBSYS available at any time.

Table 1. Titration Steps

SUBSYS DOSE	**Using**
100 mcg	1 × 100 mcg unit
200 mcg	1 × 200 mcg unit
400 mcg	1 × 400 mcg unit
600 mcg	1 × 600 mcg unit
800 mcg	1 × 800 mcg unit
1200 mcg	2 × 600 mcg unit
1600 mcg	2 × 800 mcg unit

SUBSYS Titration Process



2.3 Maintenance Dosing

Once titrated to a dose that provides adequate pain relief and tolerable side effects, patients should generally use **ONLY ONE** SUBSYS dose of the appropriate strength per breakthrough pain episode.

On those occasions when the breakthrough pain episode is not relieved within 30 minutes after administration of the SUBSYS dose, the patient may take **ONLY ONE** additional dose using the same strength for that episode.

Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with SUBSYS. Once a successful dose has been found, patients should limit consumption to four or fewer doses per day.

Dosage adjustment of SUBSYS may be required in some patients in order to continue to provide adequate relief of breakthrough pain.

If signs of excessive opioid effects appear following administration of a single SUBSYS dose, subsequent doses should be decreased.

Generally, only increase the SUBSYS dose when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.

If the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain

should be re-evaluated. In addition, if pain worsens, re-evaluate the patient for changes in the underlying pain condition.

2.4 Administration of SUBSYS

The blister package should be opened with scissors immediately prior to product use. The patient should carefully spray the contents of the unit into his or her mouth underneath the tongue.

2.5 Disposal of SUBSYS

Patients and caregivers must be advised to dispose of used unit dose systems immediately after use and any unneeded unit dose systems remaining from a prescription as soon as they are no longer needed. Consumed units represent a special risk because they are no longer protected by the child resistant blister package, yet may contain enough medicine to be fatal to a child. *[see Patient Counseling Information (17.3)]*.

A disposal bottle is provided with every carton dispensed. This container is to be used by patients or their caregivers to dispose of the contents of any unneeded unit dose systems when they are no longer needed. Instructions for usage of the disposal bottle are included in the *Medication Guide and Instructions for Use*.

2.6 Oral Mucositis

In cancer patients with mucositis, exposure to SUBSYS was greater than in patients without mucositis. For patients with Grade 1 mucositis, the increased maximum serum concentration and overall exposure requires closer monitoring for respiratory depression and central nervous system depression, particularly during initiation of therapy with SUBSYS. For patients with Grade 2 mucositis or higher, avoid use of SUBSYS unless the benefits outweigh the potential risk of respiratory depression from increased exposure. *[see Clinical Pharmacology (12.3)]*

3 DOSAGE FORMS AND STRENGTHS

SUBSYS is a sublingual spray available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths [see *How Supplied (16.3)* and *Storage and Handling (16.1)*].

4 CONTRAINDICATIONS

SUBSYS is contraindicated:

- in opioid non-tolerant patients.
- in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients.
- 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* - WARNING RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL**

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in SUBSYS. 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 Important Information Regarding Prescribing and Dispensing SUBSYS is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products.

When dispensing, DO NOT substitute a SUBSYS prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of SUBSYS compared to other fentanyl products that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of the same dose of SUBSYS for the same dose of any other fentanyl product may result in a fatal overdose.**

There are no conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.. Titrate each patient individually to provide adequate analgesia while minimizing side effects. *[See Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*

5.3 Patient/Caregiver Instructions
Patients and their caregivers must be instructed that SUBSYS contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. All used units should be disposed of immediately after use as they represent a special risk to children. *[see How Supplied/Storage And Handling (16.1, 16.2), Patient Counseling Information (17.1), and Medication Guide]*.

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.

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

5.4 Additive CNS Depressant Effects
The concomitant use of SUBSYS 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., respiratory depression, hypotension, and profound sedation). Concomitant use with strong and moderate inhibitors of CYP450 3A4 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 SUBSYS 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 SUBSYS of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease
Because potent opioids can cause respiratory depression, titrate SUBSYS with caution in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of SUBSYS may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure
Administer SUBSYS 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 SUBSYS with caution in patients with bradyarrhythmias.

5.9 MAO Inhibitors
SUBSYS 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.

5.10 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) ACCESS Program
Because of the risk of misuse, abuse, addiction and overdose [see *Drug Abuse and Dependence* (9)], SUBSYS is available only through a restricted program under a REMS 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 SUBSYS, patient and prescriber enrollment is not required.

Required components of the TIRF REMS ACCESS program are:

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

6 ADVERSE REACTIONS

6.1 Clinical Studies 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 SUBSYS has been evaluated in a total of 359 opioid-tolerant patients with breakthrough cancer pain. The duration of SUBSYS use varied during the open-label study. Safety data from a long-term extension study showed that the average duration of therapy in the open-label study was 66 days. The maximum duration of therapy was 149 days. The dose range studied in these trials ranged from 100 mcg per dose to 1600 mcg per dose.

The most commonly observed adverse reactions seen with SUBSYS are typical opioid side effects such as nausea, vomiting, somnolence, and constipation. Expect opioid side effects and manage them accordingly.

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

The most common adverse reaction leading to discontinuation of SUBSYS was nausea. There were also adverse reactions of abdominal distension, anorexia, confusional state, disorientation, somnolence, and constipation.

The clinical trials of SUBSYS were designed to evaluate safety and efficacy in treating breakthrough cancer pain; all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received SUBSYS for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain.

Table 2 lists adverse reactions with an overall frequency of 5% or greater that occurred during titration in the clinical trials. Adverse reactions are listed in descending order of frequency within each system organ class.

Table 2. Percent of Patients with Specific Adverse Events During Titration in the Clinical Trials (Events in 5% or More of Patients)

System Organ Class	Titration n=359 (%)
Gastrointestinal Disorders	
Nausea	47 (13.1%)
Vomiting	37 (10.3%)
Constipation	18 (5.0%)
Nervous System Disorders	
Somnolence	34 (9.5%)

Dizziness	26 (7.2%)

A patient was counted only once within each category.

The following adverse reactions occurred during titration in the clinical trials with an overall frequency of 1% or greater and are listed in descending order of frequency within each system organ class.
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Diarrhea, stomatitis, dry mouth
General Disorders and Administration Site Conditions: Application site irritation, pyrexia, edema peripheral, fatigue, asthenia
Metabolism and Nutrition Disorders: Decreased appetite
Nervous System Disorders: Lethargy, sedation, tremor, headache
Psychiatric Disorders: Depression, confusional state, hallucination, insomnia
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
Skin and Subcutaneous Tissue Disorders: Pruritus

The following reactions occurred during titration in the clinical trials with an overall frequency of less than 1% and are listed in descending order of frequency within each system organ class.
Eye Disorders: Vision blurred, dry eye
Gastrointestinal Disorders: Abdominal pain
Infections and Infestations: Oral candidiasis, cellulitis
Injury, Poisoning and Procedural Complications: Fall
Metabolism and Nutrition Disorders: Dehydration, anorexia
Musculoskeletal and Connective Tissue Disorders: Back pain, arthralgia, joint swelling
Psychiatric Disorders: Anxiety, agitation
Renal and Urinary Disorders: Urinary retention
Respiratory, Thoracic and Mediastinal Disorders: Cough, increased bronchial secretion, dysphonia, pharyngolaryngeal pain
Skin and Subcutaneous Tissue Disorders: Hyperhidrosis
Vascular Disorders: Hot flush

Table 3 lists adverse reactions with an overall frequency of 5% or greater for the total safety database subsequent to titration during the clinical trials.

Table 3. Adverse Reactions Subsequent to Titration in 5% or More of Patients

System Organ Class	Dosing n=269
Gastrointestinal Disorders	
Vomiting	43 (16.0%)
Nausea	28 (10.4%)
Constipation	28 (10.4%)
General Disorders and Administration Site Conditions	
Asthenia	26 (9.7%)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	28 (10.4%)
Psychiatric Disorders	
Anxiety	16 (5.9%)

A patient was counted only once within each category.

The following adverse reactions occurred during the dosing period of the clinical trial with an overall frequency of 1% or greater and are listed in descending order of frequency within each system organ class.
Blood and Lymphatic System Disorders: Anemia, neutropenia, lymphadenopathy, thrombocytopenia, leukopenia
Cardiac Disorders: Tachycardia, sinus tachycardia
Gastrointestinal Disorders: Diarrhea, stomatitis, abdominal pain, abdominal distension, gastritis, dysphagia, dyspepsia, gastroesophageal reflux disease, ascites, hematemesis
General Disorders and Administration Site Conditions: Edema peripheral, fatigue, pyrexia, chest pain, drug withdrawal syndrome, chills, irritability, malaise, application site irritation
Infections and Infestations: Oral candidiasis, pneumonia, urinary tract infection, oral herpes, gastroenteritis, laryngitis
Injury, Poisoning and Procedural Complications: Contusion
Investigations: Weight decreased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood glucose increased, blood lactate increased
Metabolism and Nutrition Disorders: Anorexia, dehydration, hypokalemia, decreased appetite, hyponatremia, hypocalcemia, hypoalbuminemia, cachexia
Musculoskeletal and Connective Tissue Disorders: Back pain, arthralgia, muscular weakness
Nervous System Disorders: Hypoesthesia, lethargy, sedation, tremor, somnolence, headache, dizziness
Psychiatric Disorders: Depression, restlessness, agitation, confusional state, insomnia, hallucination, disorientation,
Renal and Urinary Disorders: hypertension, hypotension
Respiratory, Thoracic and Mediastinal Disorders: Cough, increased bronchial secretion, wheezing, pharyngolaryngeal pain, hypoxia, dyspnea exertional
Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus

In a single-dose mucositis study, a group of patients with Grade 1 or 2 oral mucositis (n=9) and without oral mucositis (n=9) were included in a clinical trial designed to support the safety of SUBSYS. Two of the nine subjects with mucositis (one with Grade 1 and one with Grade 2) reported a burning sensation in the oral mucosa after treatment. Both of these events were considered mild and probably related to treatment. There was no change in grade of mucositis after treatment for any subject.

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when SUBSYS is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of SUBSYS with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving SUBSYS concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

The concomitant use of SUBSYS 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 SUBSYS. Patients receiving SUBSYS who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased SUBSYS activity and the dose of SUBSYS should be adjusted accordingly.

Concomitant use of SUBSYS with an MAO inhibitor, or within 14 days of discontinuation, is not recommended *[see Warnings And Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SUBSYS 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 intravenously or 160 mcg/kg subcutaneously. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for SUBSYS.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m^2 basis). 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 do not use SUBSYS during labor and delivery since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use SUBSYS 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 SUBSYS.

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 359 patients in clinical studies of SUBSYS in breakthrough cancer pain, 27% were 60 years of age and older, 17% were 65 years of age and older, and 3% were 75 years of age and older. No difference was noted in the safety profile of the group over 65 years of age as compared to younger patients in SUBSYS 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, monitor patients for respiratory depression and CNS effects when titrating SUBSYS in elderly patients.

8.6 Patients with Renal or Hepatic Impairment
Insufficient information exists to make recommendations regarding the use of SUBSYS in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via the human CYP450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, monitor patients closely for signs of respiratory and central nervous system depression.

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. SUBSYS may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction
Concerns about abuse, addiction, and diversion 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 SUBSYS may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

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

Handle SUBSYS appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

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

9.3 Dependence
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 SUBSYS 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 respiratory depression *[see Clinical Pharmacology (12.2)]*.

10.2 Immediate Management
Immediate management of opioid overdose includes 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 administer 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 SUBSYS overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access. In the presence of respiratory depression or apnea, assist or control ventilation, and administer oxygen as indicated.

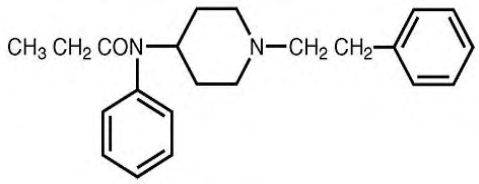
Carefully observe and appropriately manage overdosed patients until their clinical condition is well controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of SUBSYS, 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
SUBSYS (fentanyl sublingual spray) is a potent opioid analgesic intended for sublingual mucosal administration.

SUBSYS is formulated to be sprayed underneath the tongue to allow for absorption of fentanyl across the sublingual mucosa.

Active Ingredient: Fentanyl is N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide. Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 860:1) that is freely soluble in ethanol and methanol and practically insoluble in water (1:40). The molecular weight of the free base is 336.47. The pKa is 8.4. The compound has the following structural formula:



Inactive Ingredients: dehydrated alcohol 63.6%, purified water, propylene glycol, xylitol, and L-menthol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Fentanyl is an 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.

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 SUBSYS should be individually titrated to achieve the desired effect *[see Dosage And Administration (2.2)]*.

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

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

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 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 (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other

species, rats and dogs. Thyroid stimulating hormone (TSH) 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 SUBSYS. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl 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 - Warning: Importance Of Proper Patient Selection, Dosing, and Potential for Abuse, Contraindications (4), Warnings And Precautions (5.2), Adverse Reactions (6), and Overdosage (10)]*.

12.3 Pharmacokinetics

Absorption

Following the single dose administration of SUBSYS, 400 mcg, the mean absolute bioavailability of fentanyl is 76% as measured by $AUC_{0-\infty}$. Fentanyl pharmacokinetic profile and bioavailability depend on the fraction of the dose that is absorbed through the sublingual mucosa and the fraction swallowed from the gastrointestinal tract.

In a study that compared the relative bioavailability of SUBSYS and oral transmucosal fentanyl citrate [OTFC]) in 21 healthy adult subjects, the rate and extent of fentanyl absorption were considerably greater with SUBSYS [34% greater maximum plasma concentration (C_{max}) and 38% greater systemic exposure (AUC_{inf})] (Table 4 and Figure 1). *[see Dosage and Administration (2.1) and Warnings and Precautions (5.2)*].

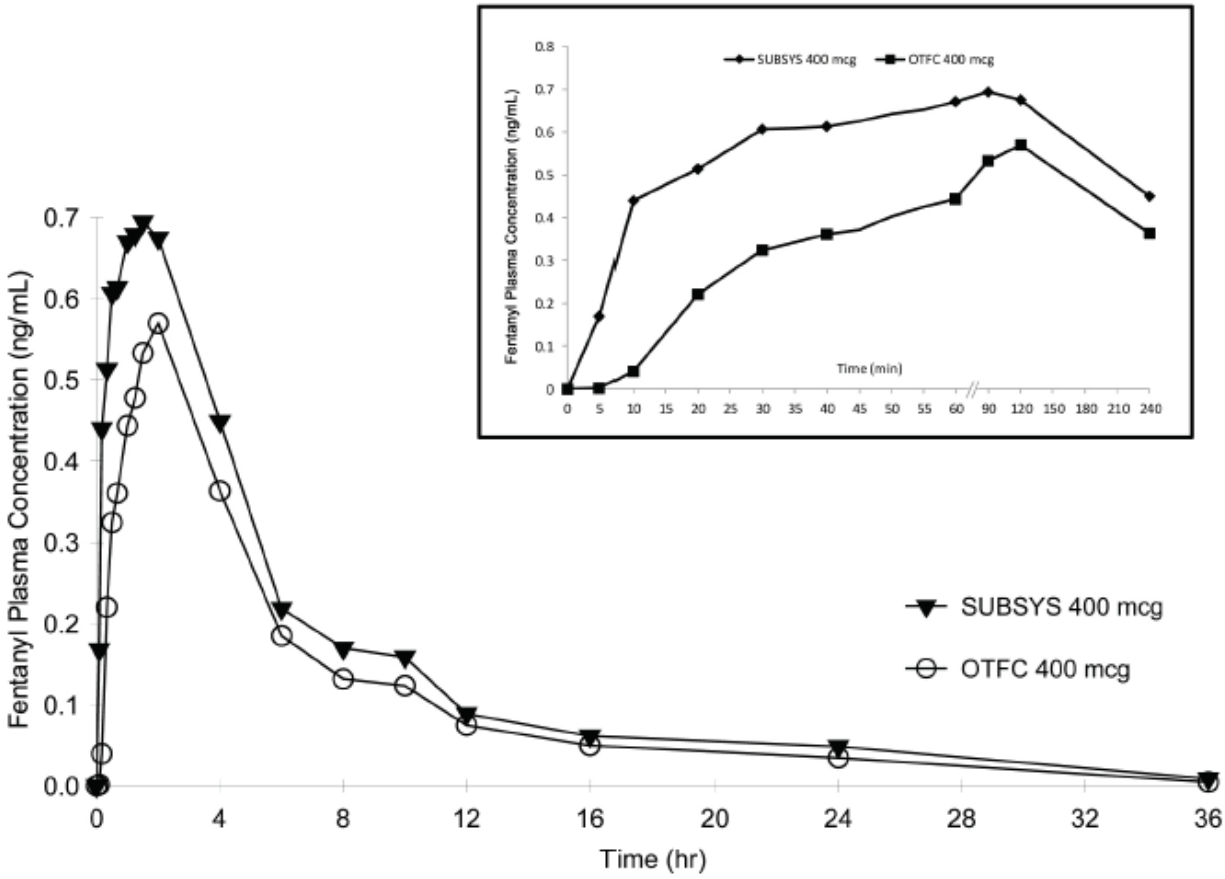
Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 4 hours.

Table 4. Pharmacokinetic Parameters of Fentanyl in Healthy Adult Subjects Receiving a Single Dose of SUBSYS or OTFC

Pharmacokinetic Parameter (Mean (CV%))	**SUBSYS 400 mcg**	**OTFC 400 mcg**
T_{max} (hour)*	1.5 (0.17, 2.00)	2.0 (0.5, 2.12)
C_{max} (ng/mL)	0.813 (31.00)	0.607 (30.48)
AUC_{0-t} (ng/mL.hr)	4.863 (35.12)	3.677 (39.16)
$AUC_{0-\infty}$ (ng/mL.hr)	5.761 (33.26)	4.182 (39.93)

* Data for T_{max} presented as median (range)

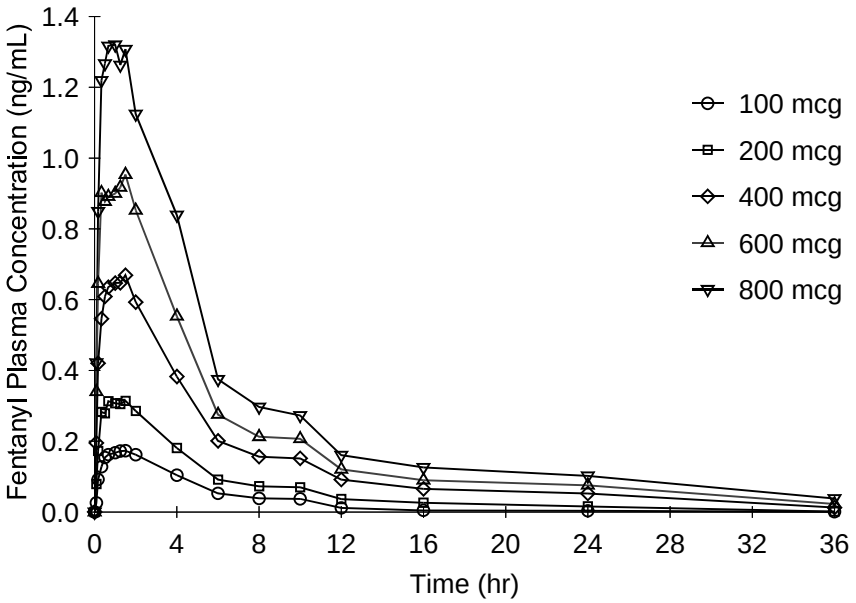
Figure 1
Mean Fentanyl Plasma Concentration-Time Profiles Following Single Dose Administration of SUBSYS 400 mcg and OTFC 400 mcg in Healthy Adult Subjects



Neither peak fentanyl concentration nor total exposure was appreciably affected by the pretreatment of oral cavity with hot water or refrigerated iced water, low or high pH beverages when SUBSYS was administered under fasted condition.

Dose proportionality among the five available strengths of SUBSYS (100, 200, 400, 600, and 800 mcg) has been evaluated in a crossover study in healthy subjects. Mean plasma fentanyl levels following these five dose levels of SUBSYS are shown in Figure 2. The curves for each dose level are similar in shape with increasing dose levels producing increasing plasma fentanyl levels. The C_{max} and $AUC_{0-\infty}$ values increased in a dose-dependent manner that is approximately proportional to the SUBSYS doses administered.

Figure 2.
Mean Fentanyl Plasma Concentration-Time Profiles (36 hours) after Administration of SUBSYS 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg in Healthy Subjects



The pharmacokinetic parameters of the five strengths of SUBSYS tested are shown in Table 5. The mean C_{max} ranged from 0.202 – 1.610 ng/mL. The median time of maximum plasma concentration (T_{max}) across these five doses of SUBSYS varied from 0.67 - 1.25 hours (range of 0.08 – 4.00 hours) as measured after the start of administration.

Table 5. Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects Receiving Single Doses of 100, 200, 400, 600, 800 mcg of SUBSYS

Pharmacokinetic Parameter (Mean (%CV))	**100 mcg**	**200 mcg**	**400 mcg**	**600 mcg**	**800 mcg**
T_{max} (hr)*	1.25 (0.17-2.05)	1.25 (0.17-2.03)	1.00 (0.17-2.03)	0.67 (0.08-2.00)	0.69 (0.17-4.00)
C_{max} (ng/mL)	0.202 (28.35)	0.378 (29.69)	0.800 (27.66)	1.17 (32.48)	1.610 (37.22)
AUC_{last} (ng/mL·hr)	0.9776 (49.82)	1.985 (40.93)	4.643 (44.53)	6.682 (32.46)	9.450 (36.62)
$AUC_{0-\infty}$ (ng/mL.hr)	1.245 (53.82)	2.475 (46.48)	5.342 (44.16)	7.446 (81.54)	10.38 (35.60)
$T_{1/2}$ (hr)	5.25 (89.92)	8.45 (77.94)	11.03 (62.20)	10.64 (41.73)	11.99 (32.15)

* Data for T_{max} presented as median (range)

The effect of mucositis (Grades 1 and 2) on the pharmacokinetics of SUBSYS was studied in a group of cancer patients with mucositis (N = 7 for Grade 1 and N = 2 for Grade 2) and without mucositis (N = 8). A single 100 mcg dose was administered. Mean summary statistics (standard deviation in parentheses) for patients with Grade 1 mucositis and patients without mucositis are presented in Table 6. Cancer patients with Grade 1 mucositis exhibited 73% greater C_{max} and 52% greater AUC_{last} values in comparison to patients without mucositis. The two cancer patients with Grade 2 mucositis had 4- and 7-fold higher C_{max} and $\geq$3- fold higher AUC_{last} values compared to patients without mucositis.

Monitor patients with Grade 1 mucositis closely for signs of respiratory and central nervous system depression particularly during initiation of therapy with SUBSYS. As a result of the large and variable increase in exposure of fentanyl, use of SUBSYS should be avoided in patients with Grade 2 and more severe mucositis unless the benefits are expected to outweigh the risk of respiratory depression.

Table 6. Mean (%CV) Pharmacokinetic Parameters in Patients with Mucositis

Patient Status	N	C_{max} (ng/mL)	T_{max} (hr)*	$AUC_{0\text{-last}}$ (ng/mL.hr)
Mucositis Grade 1	**7**	**0.45 (95.56)**	**0.25 (0.25, 2.00)**	**1.38 (44.93)**
No Mucositis	**8**	**0.26 (57.69)**	**0.38 (0.25, 2.00)**	**0.91 (14.29)**

* Data for T_{max} presented as median (range)

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 (Vss) was 4 L/kg.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 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 - 0.7 L/hr/kg). The terminal half-life after SUBSYS administration is from 5 to 12 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 intravenously and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for SUBSYS.

14 CLINICAL STUDIES

The efficacy of SUBSYS was demonstrated in a double-blind, placebo-controlled, crossover study in opioid tolerant adult patients with cancer and breakthrough pain. The dose range studied was from 100 mcg per dose to 1600 mcg per dose. Patients entering the trial must have had on average 1-4 episodes of pain per day not controlled on stable, chronic maintenance doses of opioid medication of at least 60 mg/day of morphine, 25 mcg/hr of transdermal fentanyl, or an equianalgesic dose of another opioid for at least 7 days.

The study began with an open-label dose titration period followed by a double-blind treatment period. The goal of titration was to find the dose of SUBSYS that provided adequate analgesia with acceptable side effects. Patients were titrated from a 100 mcg starting dose. Once a successful dose was established, patients were enrolled into the double-blind period and randomized to a sequence of 10 treatments; 7 with SUBSYS and 3 with placebo.

Patients assessed pain intensity on a 100 mm visual analog scale that rated the pain as 0=none to 100=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-100) was then measured at 5, 10, 15, 30, 45 and 60 minutes after the start of administration. The summed pain intensity difference from baseline to 30 minutes after dosing was the primary efficacy measure.

Out of 130 patients who entered the titration phase, 98 (75%) were able to titrate to a dose that adequately reduced pain with tolerable side effects and entered into the double-blind period.

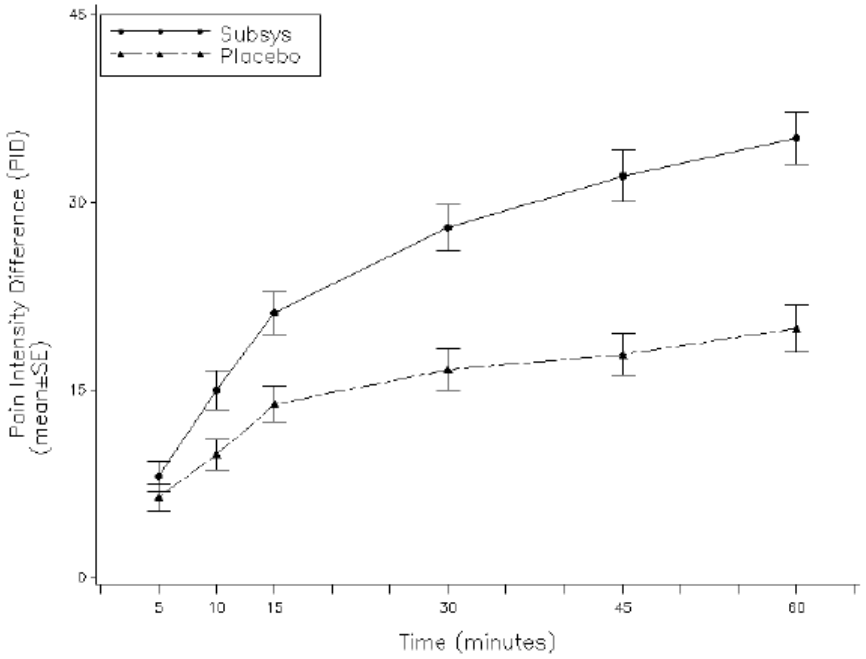
The breakdown of successful dose for the patients entering the double-blind period of the study is as follows:

SUBSYS Dose	**Total No. (%) n=96**
100 mcg	4 (4%)
200 mcg	7 (7%)
400 mcg	14 (15%)
600 mcg	15(16%)
800 mcg	23 (24%)
1200 mcg (2 × 600 mcg)	20 (21%)
1600 mcg (2 × 800 mcg)	13 (14%)

SUBSYS produced a statistically significantly greater reduction in pain intensity compared to placebo as measured by the Summed Pain Intensity Differences scale (SPID) at 30 minutes.

The primary outcome measure, the mean sum of the pain intensity difference at 30 minutes (SPID30), was statistically significantly higher for SUBSYS than for placebo. The difference in mean pain intensity based on a 100 mm visual analog scale is displayed in Figure 3.

Figure 3
Pain Intensity Differences over Time



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

SUBSYS is supplied in individually sealed blister packages. Store at 20-25°C (68-77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use. [See USP Controlled Room Temperature.] Do not use if the blister package has been opened.

16.2 Disposal of SUBSYS

Patients and caregivers must be advised to dispose of used unit doses systems immediately after use and any unneeded unit dose systems remaining from a prescription as soon as they are no longer needed. Consumed units represent a special risk because they are no longer protected by the blister package, yet may contain enough medicine to be fatal to a child. *[see Patient Counseling Information (17.3)]*.

A disposal bottle is provided with every carton dispensed. *[see Patient Counseling Information (17.4)]*. This container is to be used by patients or their caregivers to dispose of the contents of any unneeded unit dose systems when they are no longer needed. Instructions for usage of the disposal bottle are included in the *Medication Guide.*

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed.

Instructions for disposal are also included in *Disposal of Used SUBSYS Unit Dose Systems (17.3)* and *Disposal of Unopened SUBSYS Unit Dose Systems When No Longer Needed (17.4)* and in the *Medication Guide*. If additional assistance is required, call Insys Therapeutics, Inc. at 1-877-978-2797.

16.3 How Supplied

Each SUBSYS carton contains individual blister packages containing single spray units of SUBSYS, a supply of small white disposal bags for disposing of used SUBSYS units, a Medication Guide and a Package Insert. In addition to your supply of SUBSYS spray units, you will be given a separate carton containing a disposal bottle, a large disposal bag, and a Medication Guide. SUBSYS is supplied in individually sealed, protective blister packages. These blister packages are packed into 6 per shelf carton for use when patients are initially titrating to an appropriate dose and 14 and 28 per shelf cartons after patients have titrated to the appropriate dose.

Each unit dose system consists of a white actuator attached to a light purple vial holder. The dosage strength is marked on the label on the actuator, the blister package and the shelf carton. See the protective blister package and shelf carton for product information.

Dosage Strength (fentanyl base)	**Carton/Blister Package Color**	**NDC Number**
100 mcg	Blue	20482-001-06
		20482-001-14
		20482-001-28
200 mcg	Green	20482-002-06
		20482-002-14
		20482-002-28
400 mcg	Magenta (Pink)	20482-004-06
		20482-004-14
		20482-004-28
600 mcg	Purple	20482-006-06
		20482-006-14
		20482-006-28
800 mcg	Orange	20482-008-06
		20482-008-14
		20482-008-28

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling *(Medication Guide)*.

17.1 Patient/Caregiver Instructions

Before initiating treatment with SUBSYS, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time SUBSYS is dispensed because new information may be available.

- Outpatients must be enrolled in the TIRF REMS Access program before they can receive SUBSYS.
- Allow patients the opportunity to ask questions and discuss any concerns regarding SUBSYS or the TIRF REMS Access program.
- As a component of the TIRF REMS Access program, prescribers must review the contents of the SUBSYS Medication Guide with every patient before initiating treatment with SUBSYS.
- Advise the patient that SUBSYS 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 SUBSYS.
- Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of SUBSYS.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program.

1. **Patients and their caregivers must be instructed that children exposed to SUBSYS are at high risk OF FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep SUBSYS out of the reach of children *[See How Supplied/Storage And Handling (16.1), Warnings And Precautions (5.2 and 5.3) and Medication Guide for specific patient instructions.]*
2. Provide patients and their caregivers with a *Medication Guide* each time SUBSYS is dispensed because new information may be available.
3. Instruct patients and their caregivers to keep both used and unused dosage units out of the reach of children. Consumed units must be properly disposed of as soon as possible *[see How Supplied/Storage And Handling (16.1), Warnings And Precautions (5.3), and Patient Counseling Information (17.3* and *17.4)]*.
4. Instruct patients not to take SUBSYS 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.
5. Instruct patients on the meaning of opioid tolerance and that SUBSYS is only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.
6. Instruct patients that, if they are not taking an opioid medication on a scheduled basis (around-the-clock), they should not take SUBSYS.
7. Instruct patients that, if the breakthrough pain episode is not relieved 30 minutes after administration, they may take **ONLY ONE ADDITIONAL DOSE OF SUBSYS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take no more than two doses of SUBSYS for any breakthrough pain episode.**
8. Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.
9. Instruct patients NOT to share SUBSYS and that sharing SUBSYS with anyone else could result in the other individual's death due to overdose.
10. Make patients aware that SUBSYS contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
11. Instruct patients that the active ingredient in SUBSYS, fentanyl, is a drug that some people abuse. SUBSYS should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.
12. Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking SUBSYS.
13. Instruct patients to use SUBSYS exactly as prescribed by their doctor and not to take SUBSYS more often than prescribed.
14. Caution patients that SUBSYS can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking SUBSYS of these dangers and counsel them accordingly.
15. Warn patients to not combine SUBSYS with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

16. Inform female patients that if they become pregnant or plan to become pregnant during treatment with SUBSYS, they should ask their doctor about the effects that SUBSYS (or any medicine) may have on them and their unborn children.

17.2 SUBSYS Child Safety Kit

Provide patients and their caregivers with a SUBSYS Child Safety Kit. The kit consists of a safe interim storage bag, a lock for the bag and contains a package of cabinet and drawer child safety latches for securing the storage space at home to help patients store SUBSYS and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, health care professionals can call Insys Therapeutics, Inc., at 1-877-978-2797.

17.3 Disposal of Used SUBSYS Unit Dose Systems

Patients must be instructed to safely dispose of used SUBSYS units.

1. After administration of SUBSYS, place the used spray unit into one of the disposable bags provided with your prescription.
2. Seal the bag and discard into a trash container out of the reach of children.

17.4 Disposal of Unopened SUBSYS Unit Dose Systems When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unopened SUBSYS units:

1. Using a pair of scissors, cut the blister package on the line marked by an image of a pair of scissors and the instruction “cut to open” printed on the blister. Peel back the blister material to remove the SUBSYS unit from the package.
2. Remove the disposal bottle provided in the individual carton with your prescription and flip up the top of the cap.
3. Position the nozzle of the unused spray unit upside-down into the opening of the bottle and push through the insert.
4. Hold the disposal bottle down with one hand while pressing the light purple vial holder with your thumb downwards to expel the liquid from the nozzle directly into the bottle opening. This procedure should be repeated for each unopened SUBSYS unit.
5. Flip down the top of the disposal bottle to close and shake.
6. After all unopened spray units provided with your prescription have been expelled into the disposal bottle, place the disposal bottle into the bag provided.
7. Seal the bag and discard into a trash container out of the reach of children.
8. Place each used spray unit into one of the disposable bags provided with your prescription.
9. Seal the bag and discard into a trash container out of the reach of children.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of SUBSYS are provided in the SUBSYS *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 unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for Insys Therapeutics, Inc. (1-877-978-2797) or seek assistance from their local DEA office.