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: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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) 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 Pharmacology (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 (5.10)]* 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

SUBSYS is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.)

Patients on Actiq

The initial dose of SUBSYS is always 100 mcg with the only exception of patients already using Actiq.

a. For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patients on Actiq table below (Table 1). Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on ACTIQ

Current ACTIQ Dose (mcg)	Initial SUBSYS Dose (mcg)
200	100 mcg spray
400	100 mcg spray
600	200 mcg spray
800	200 mcg spray
1200	400 mcg spray
1600	400 mcg spray

b. For patients converting from ***Actiq doses 400 mcg and below***, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength.

c. For patients converting from ***Actiq doses of 600 and 800 mcg,*** titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength.

d. For patients converting from ***Actiq doses of 1200 and 1600 mcg***, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength.

All Other Patients

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.

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