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

- **Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. 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. (5.1)**
- **Accidental ingestion of SUBSYS, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (5.2)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7, 12.2)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to SUBSYS. (2.3, 5.5)**
- **When dispensing, do not substitute with any other fentanyl products. (5.5)**
- **SUBSYS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.6)**
- **SUBSYS is available only through a restricted program called the TIRF REMS. Pharmacies, outpatients, and healthcare professionals who prescribe to outpatients are required to enroll in the program. Patients must be opioid tolerant to receive a TIRF medicine (5.7)**
- **Prolonged use of SUBSYS during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)**

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

Boxed Warning	03/2021
Dosage and Administration (2.2)	03/2021
Warnings and Precautions (5.1, 5.4, 5.6, 5.7)	03/2021

----------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 around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

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

Limitations of Use (1):

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency room
- As a part of the Transmucosal Immediate-Release Fentanyl (TIRF) REMS, SUBSYS may be dispensed by outpatient pharmacies only to outpatients enrolled in the program (5.7). For inpatient administration of SUBSYS, patient and prescriber enrollment are not required.

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

- Patients must require and use around-the-clock opioids when taking SUBSYS. (1)
- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with SUBSYS. Consider prescribing naloxone based on the patient's risk factors for overdose [2.2, 5.1, 5.4, 5.6].
- Initiate treatment with 100 mcg except patients already using Actiq. (2.3)
- Individually titrate to a tolerable dose that provides adequate analgesia using a single SUBSYS dose per breakthrough cancer pain episode. (2.5)
- No more than two doses can be taken per breakthrough pain episode. (25)
- Wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS. (2.5)
- Limit consumption to four or fewer doses per day once successful dose is found. (2.5)
- When opioid therapy is no longer required, consider discontinuing SUBSYS along with a gradual downward titration of other opioids to minimize possible withdrawal effects. (2.6).

----------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, or in emergency department. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl, or components of SUBSYS. (4)

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

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

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

Most common adverse reactions during treatment (incidence ≥ 5%): vomiting, nausea, constipation, dyspnea, and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact West Therapeutic Development, LLC., at 1-844-452-9263 or FDA at 1-800-FDA-1088 or *www.fda.gov/ medwatch.*

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Life-Threatening Respiratory Depression

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

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. *[see Contraindications (4)]*

Accidental Ingestion

Accidental ingestion of even one dose of SUBSYS especially by children, can result in a fatal overdose of fentanyl *[see Warnings and Precautions (5.2)]*.

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 Warnings and Precautions (5.2); How Supplied/Storage and Handling (16)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of SUBSYS with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving SUBSYS and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.3), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

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

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

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of 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 *[see Dosage and Administration (2.1), Warnings and Precautions (5.5)]*.

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

Addiction, Abuse, and Misuse

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

Risk Evaluation and Mitigation Strategy (REMS)

Because of the risk for accidental exposure, misuse, abuse, addiction, and overdose, SUBSYS is available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS, pharmacies, outpatients, and healthcare professionals who prescribe to outpatients must enroll in the program. Inpatient pharmacies must develop policies and procedures to verify opioid tolerance in inpatients who require SUBSYS while hospitalized *[see Warnings and Precautions (5.7)]*. Further information is available at www.TIRFREMSaccess.com or by calling 1-866-822-1483.

Neonatal Opioid Withdrawal Syndrome

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

1. INDICATIONS AND USAGE

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

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

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency room *[see Contraindications (4)]*.
- As part of the Transmucosal Immediate-Release Fentanyl (TIRF) REMS, SUBSYS may be dispensed by outpatient pharmacies only to outpatients enrolled in the program. *[see Warnings and Precautions (5.7)]*. For inpatient administration of SUBSYS, patient and prescriber enrollment are not required.

2. DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

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