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 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

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

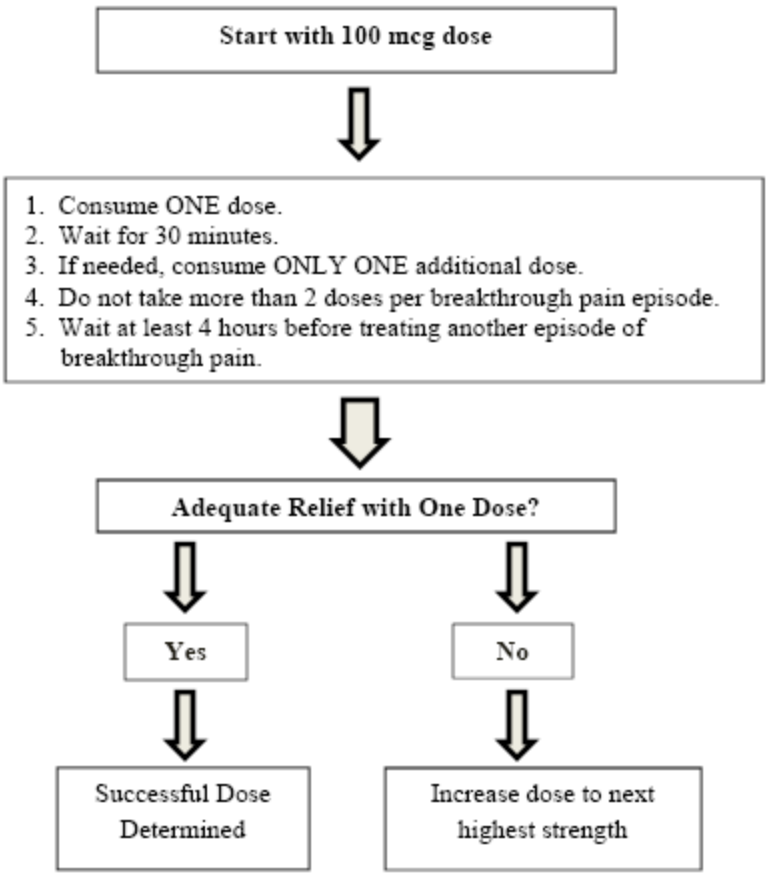
a. From the 100 mcg initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single SUBSYS dose per breakthrough cancer pain episode with tolerable side effects. Patients should record their use of SUBSYS over several 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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.