

EXHIBIT 1008

ACTIQ[®]

(oral transmucosal fentanyl citrate)

CII

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

***Actiq* is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, *Actiq* is contraindicated in the management of acute or postoperative pain. This product **must not** be used in opioid non-tolerant patients.

Actiq 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.

Patients and their caregivers must be instructed that *Actiq* contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep all units out of the reach of children and to discard opened units properly. (See Information for Patients and Their Caregivers for disposal instructions.)

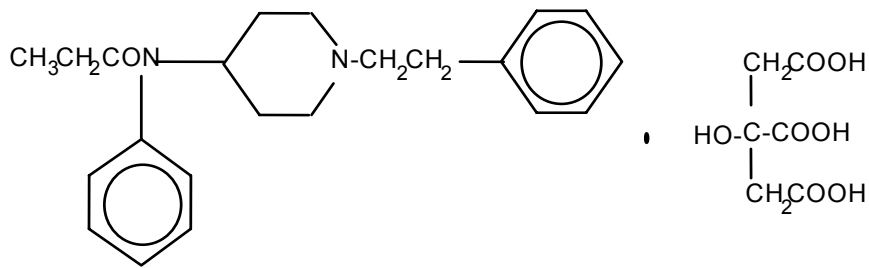
WARNING: May be habit forming

DESCRIPTION

Actiq (oral transmucosal fentanyl citrate) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. *Actiq* is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed.

Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the *Actiq* unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



Actiq is available in six strengths equivalent to 200, 400, 600, 800, 1200, or 1600 mcg fentanyl base that is identified by the text on the solid drug matrix, the dosage unit handle tag, the blister package, and the shelf carton.

Inactive Ingredients: Hydrated dextrans, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology:

Fentanyl, a pure opioid agonist, acts primarily through interaction with opioid mu-receptors located in the brain, spinal cord and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). The most clinically useful pharmacologic effects of the interaction of fentanyl with mu-receptors are analgesia and sedation.

Other opioid effects may include somnolence, hypoventilation, bradycardia, postural hypotension, pruritus, dizziness, nausea, diaphoresis, flushing, euphoria and confusion or difficulty in concentrating at clinically relevant doses.

Clinical Pharmacology

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 opioid non-tolerant individuals, fentanyl provides effects ranging from analgesia at blood levels of 1 to 2 ng/mL, all the way to surgical anesthesia and profound respiratory depression at levels of 10-20 ng/mL.

In general, the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance to any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of *Actiq* should be individually titrated to achieve the desired effect (see **DOSAGE AND ADMINISTRATION**).

Gastrointestinal (GI) Tract and Other Smooth Muscle:

Opioids increase the tone and decrease contractions of the smooth muscle of the gastrointestinal (GI) tract. This results in prolongation in GI transit time and may be responsible for the constipating effect of opioids. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the overall effect tends to vary, in some cases producing urinary urgency, in others, difficulty in urination.

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 *Actiq*. In studies of opioid non-tolerant subjects, respiratory rate and oxygen saturation typically decrease as fentanyl blood concentration increases. Typically, peak respiratory depressive effects (decrease in respiratory rate) are seen 15 to 30 minutes from the start of oral transmucosal fentanyl citrate (OTFC[®]) administration and may persist for several hours.

Serious or fatal respiratory depression can occur, even at recommended doses, in vulnerable individuals. As with other potent opioids, fentanyl has been associated with cases of serious and fatal respiratory depression in opioid non-tolerant individuals.

Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with *Actiq* 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 BOX WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and OVERDOSAGE for additional information on hypoventilation.)

Pharmacokinetics**Absorption:**

The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

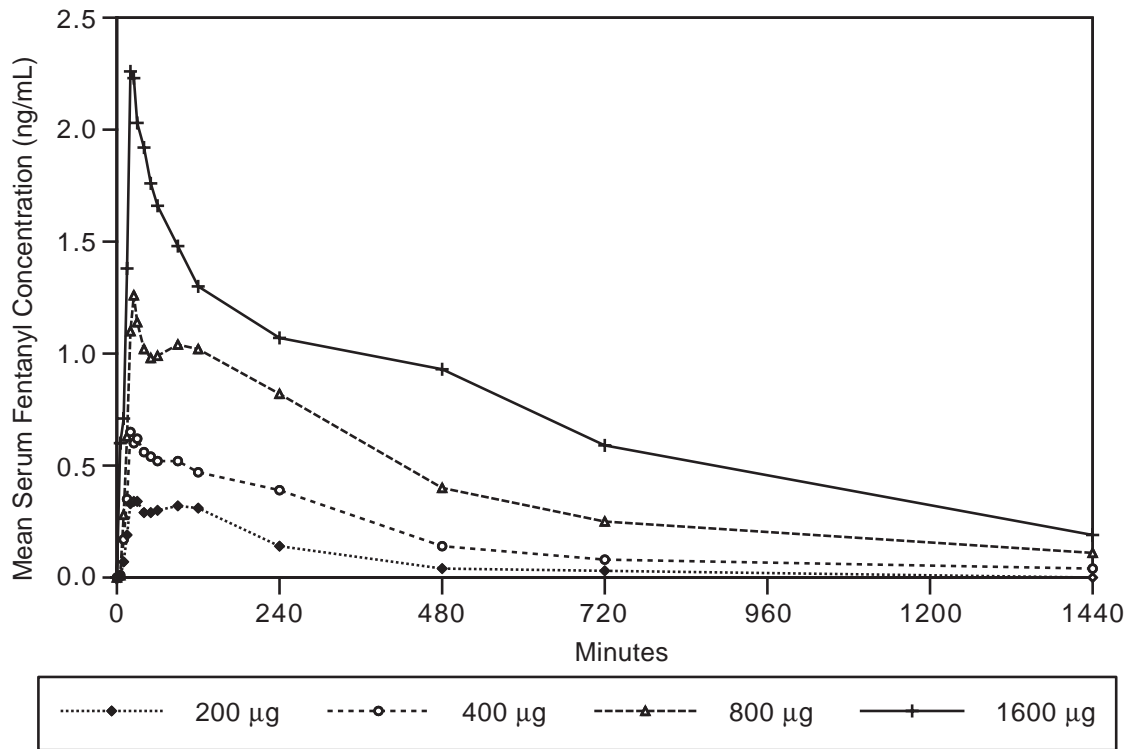
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

Normally, approximately 25% of the total dose of *Actiq* is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of *Actiq* is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit dose of *Actiq*, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

Dose proportionality among four of the available strengths of *Actiq* (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects. Mean serum fentanyl levels

in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0 \rightarrow \infty}$ increased in a dose-dependent manner that is approximately proportional to the *Actiq* administered.

Figure 1.
Mean Serum Fentanyl Concentration (ng/mL)
in Adult Subjects Comparing 4 Doses of *Actiq*



The pharmacokinetic parameters of the four strengths of *Actiq* tested in the dose-proportionality study are shown in Table 1. The mean C_{max} ranged from 0.39 - 2.51 ng/mL. The median time of maximum plasma concentration (T_{max}) across these four doses of *Actiq* varied from 20 - 40 minutes (range of 20-480 minutes) as measured after the start of administration.

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.