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APPLICATION NUMBER:

202788Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 202788	Submission Date(s): March 4, 2011
Proposed Brand Name	SUBSYS™
Generic Name	Fentanyl Sublingual Spray
Reviewer	Wei Qiu, Ph. D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Insys Therapeutics, Inc
Relevant IND(s)	72,411
Submission Type	505(b)(2), original
Formulation; Strength(s)	Sublingual Spray for transmucosal delivery; 100, 200, 400, 600, and 800 mcg
Dosing regimen	Initial dose of 100 mcg; then titrate to a tolerable dose
Indication	Management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying cancer

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA 202788 submitted on March 4, 2011 and finds it acceptable from clinical pharmacology perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Insys submitted this 505(b)(2) NDA for Fentanyl Sublingual Spray, 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg for the management of breakthrough cancer pain (b)(4) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Sponsor proposed to rely on the Agency's previous finding of the safety and efficacy of Actiq® fentanyl citrate oral transmucosal lozenge (NDA 020747).

Fentanyl is an opioid agonist and available as injectable, transdermal, nasal spray, and transmucosal (oral transmucosal lozenge (Actiq® NDA 20747), buccal tablet (Fentora® NDA 21947), buccal film (Onsolis®, NDA 22266), and sublingual tablet (Abstral® NDA 22510)) formulations. This current submission is for fentanyl sublingual spray.

The clinical and clinical pharmacology database for this NDA consists of one efficacy/safety study (INS-05-001), one open-label safety study (INS-06-007), and four clinical pharmacology studies. These clinical pharmacology studies include (1) pilot ascending single dose PK study in healthy male subjects (FNY-P4-270), (2) single dose

relative bioavailability study in comparison to Actiq® transmucosal lozenge and Fentanyl Citrate Injection in healthy subjects (INS-06-003), (3) a single dose crossover study to evaluate Fentanyl Sublingual Spray dose proportionality and to evaluate the potential effects of temperature and pH on relative bioavailability in healthy subjects (INS-06-004), and (4) a single dose PK study in opioid tolerant cancer patients with and without mucositis (Study INS-09-011). This review focused on Studies INS-06-003, INS-06-004, and INS-09-011. The pilot study FNY-P4-270 was not thoroughly reviewed (b) (4) and the dose levels were further studied in a more comprehensive Study INS-06-004.

Absolute Bioavailability:

The mean absolute bioavailability of Fentanyl Sublingual Spray 400 mcg in comparison to fentanyl citrate intravenous injection 100 mcg was 72.1% and 75.6% based dose normalized AUClast and AUCinf values, respectively.

Relative Bioavailability as Compared to Actiq®:

Single dose of the 1 x 400 mcg fentanyl sublingual spray exhibits 34% and 36% greater Cmax and AUCinf values as compared to Actiq® 1 x 400 mcg under fasting condition. The point estimates of the geometric mean ratio (Fentanyl Sublingual Spray 400 mcg/Actiq® 400 mcg) for Cmax, AUClast, and AUCinf are 133.67%, 133.44% and 136.27%, respectively. The corresponding 90% confidence intervals are 119.67% – 149.31%, 121.47% – 146.58%, and 121.21% – 153.20%, respectively.

Dose Proportionality:

The systemic exposure of fentanyl increased in an approximate dose proportional manner over the 100 mcg – 800 mcg range under fasting condition based on the ANOVA and linear regression of the dose-normalized Cmax, AUClast, and AUCinf values. When each lower strength (100 mcg, 200 mcg, 400 mcg, and 600 mcg) was compared to the highest strength 800 mcg, ANOVA analysis showed that for Cmax/Dose, all the 90% confidence interval fell within the 80-125% range except for the 600 mcg strength (lower bound of the 90% confidence interval was 79.47%). For AUCinf/Dose, all 90% confidence interval fell within the 80-125% limit except for the 100 mcg strength (lower bound of the 90% confidence interval was 77.44%). For AUClast/Dose, the 90% confidence interval for the 400 mcg and 600 mcg fell within the

80-125% while the lower bounds for the 100 mcg and 200 mcg were 67.95% and 76.95%, respectively.

Linear regression results showed that the slopes for Cmax/Dose and AUCinf/Dose were not significant different from 0. The value of the slope for AUClast/Dose (2.89 E-04) was 2.89 E-04 significant different from zero, however, the value is very close to zero.

Effect of pretreatment of oral cavity with beverages which have different temperatures and pH levels:
The pretreatment of oral cavity with hot water did not affect the PK of fentanyl sublingual spray. The Cmax, AUClast, AUCinf values after pretreatment with hot water were bioequivalent to the reference (no pretreatment) based on the 90% confidence interval (81.70% – 114.76% for Cmax; 83.71% – 113.03% for AUClast; 85.87% – 119.38% for AUCinf) falling within the 80-125% limits. The cold water decreased the AUC values of fentanyl by 5 to 8% and had no effect on fentanyl Cmax values. The point estimate of the geometric mean ratio (cold water/no pretreatment) for Cmax, AUClast and AUCinf are 100.08%, 94.78%, and 92.23%, respectively. The corresponding 90% confidence interval is 83.07% – 120.58%, 75.95% – 118.29%, and 73.38% – 115.93%, respectively.

The pretreatment of oral cavity with low pH beverage decreased fentanyl Cmax by 17% but had no effect on the AUC values. The point estimate of the geometric mean ratio (low pH/no pretreatment) for Cmax, AUClast, and AUCinf are 83.26%, 91.93%, and 95.68%, respectively. The corresponding 90% confidence intervals are 70.81% - 97.90%, 81.70% - 103.44%, and 84.39% - 108.49%, respectively. The pretreatment of oral cavity with high pH beverage increased fentanyl Cmax, AUClast, and AUCinf by 23%, 19%, and 18%, respectively.

Effect of Mucositis:
In opioid tolerant cancer patients with Grade 1 mucositis, mean fentanyl Cmax and AUClast values were 73% and 52% greater than the patients without mucositis following the administration of 100 mcg fentanyl sublingual spray. In the two patients with Grade 2 mucositis (subject 804 and 910), fentanyl Cmax values were 7-fold and 4-fold greater than the mean Cmax values obtained in patients without mucositis for subject 804 and subject 910, respectively. The corresponding fentanyl AUClast values were 17-fold and

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