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## Single- and Repeat-Dose Pharmacokinetics of Sublingual Sufentanil NanoTab in Healthy Volunteers

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**Introduction:** Patient-controlled analgesia (PCA) using intravenous opioids is currently the most common approach to the treatment of moderate-to-severe post-operative pain. The invasive route of delivery coupled with the complex set-up and programming of these IV PCA systems can be problematic. Moreover, morphine is the most commonly used opioid with these systems and its active metabolites, morphine-3-glucuronide and morphine-6-glucuronide, can accumulate in the post-operative setting, resulting in a prolonged duration of action and untoward side-effects. The Sublingual Sufentanil NanoTab™ to be delivered from a hand-held, pre-programmed, PCA device is a novel, non-invasive approach to management of pain in the post-operative setting. Sufentanil has no active metabolites and in preclinical toxicology studies, sufentanil has a high therapeutic index (80-fold and 300-fold higher than fentanyl and morphine, respectively). Although sufentanil has a higher lipophilicity than fentanyl, it has a lower volume of distribution and a shorter terminal half-life. Long-term administration of sufentanil over the course of hours or days does not result in a significantly prolonged context-sensitive half-time, in contrast to fentanyl, further supporting the use of sufentanil for post-operative analgesia.

**Methods:** Two Phase 1 studies of Sublingual Sufentanil NanoTabs have been conducted in healthy young volunteers to evaluate the pharmacokinetic profile of both single- and repeat-dosing. A total of 33 subjects (17 males, 16 females, 18-45 years old) in both studies received a single 10 mcg dose of the Sufentanil NanoTab and 12 of these 33 subjects in a separate arm received a 10 mcg dose every 20 minutes for a total of four doses. Bioavailability was calculated using a comparator arm consisting of a short intravenous infusion (10 or 20 minutes) of sufentanil 5 mcg in both studies.

**Results:** An analysis of the data from our Phase 1 studies to date using the 10 mcg dosage strength of the Sublingual Sufentanil NanoTab demonstrated that the Sufentanil NanoTab bioavailability averaged 78%,  $C_{max}$  mean value was  $21.4 \pm 7.8$  pg/ml (coefficient of variation, CV = 36%),  $T_{max}$  mean value was  $43.8 \pm 15$  minutes (CV = 34%) and  $T_{1/2}$  averaged  $2.1 \pm 0.8$  hours. Repeat dosing of the 10 mcg dosage strength every 20 minutes for a total of four doses (dosing time = 0, 20, 40 and 60 minutes) resulted in an absolute bioavailability of 88% and both a highly consistent  $C_{max}$  of  $78.7 \pm 20.1$  pg/ml (CV = 26%) and  $T_{max}$  of  $84 \pm 15$  minutes (CV = 18%), which occurred 24 minutes following the last dosing at 60 minutes. No sublingual irritation due to NanoTab dosing was observed throughout these studies.

**Conclusions:** Sublingual Sufentanil NanoTab pharmacokinetic parameters (relatively high absolute bioavailability,  $C_{max}$  and  $T_{max}$  with low variability, and a relatively short half-life) are desirable for use as a titratable analgesic in the post-operative setting. The highly consistent and shortened  $T_{max}$  with repeat-dosing indicates that safe and reliable redosing in the clinical setting is achievable with this product. Multicenter Phase II clinical trials in patients following major orthopedic and major abdominal surgery have recently been completed and further demonstrate the clinical safety and efficacy of Sublingual Sufentanil NanoTabs in post-operative pain management.

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