EXECUTIVE SUMMARY OF CLINICAL AND CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEWS

Date of Submission:	**November 25, 2002**
Type of Submission:	**Supplement to NDA 19-813 for Pediatric Exclusivity Determination**
Product:	**DURAGESIC® (fentanyl transdermal system)**
Sponsor:	**ALZA**
Review Date:	**May 15, 2003**
Medical Team Leader:	**Sharon Hertz, M.D.**
Medical Officer:	**Dawn Elizabeth McNeil, M.D.**
Clinical Pharmacology and Biopharmaceutics Reviewer:	**David Lee, Ph.D.**
Pharmacometrics Consultant:	**He Sun, Ph.D.**
Project Manager:	**Kimberly Compton, Pharm.D.**

EXECUTIVE SUMMARY

DURAGESIC® (fentanyl transdermal patch, NDA 19-813) is an opioid analgesic that was originally approved in August 1990, for use in patients over the age of 12 years. DURAGESIC® is indicated for treatment of chronic pain (such as that of malignancy) that cannot be managed by lesser means such as acetaminophen-opioid combination, NSAIDs, or PRN dosing with short-acting opioids, and that requires continuous opioid administration.

The current supplement was submitted November 25, 2002 in response to a pediatric written request issued by the Agency on July 15, 1999 and amended on November 1, 1999 and February 22, 2001. The objectives of the written request were to evaluate the safety of initiating and continuing treatment with the fentanyl transdermal system in an opioid-tolerant pediatric patient population with chronic pain, to determine the pharmacokinetics of the fentanyl transdermal system in the same pediatric patient population, and to determine an appropriate dosing regimen.

The sponsor has met the objectives of the written request having demonstrated a safe method for converting patients to DURAGESIC from a prior opioid and a safe method for dose titration, and having provided an evaluation of the pharmacokinetics of DURAGESIC® in pediatric patients.

Dosing, titration, and safety information was obtained from Study FEN-USA-87, submitted to fulfill the requirements of the written request, with additional data from studies FEN-INT-24 and FEN-GBR-14. All three of these were open-label, two-week, multiple-dose studies of the safety and pharmacokinetics of DURAGESIC® in the pediatric patient population.

In Studies FEN-USA-87 and FEN-GBR-14 patients were converted to DURAGESIC® based on their opioid analgesic requirement over the previous 24 hours. In Study FEN-INT-24 all patients initiated therapy with an investigational DURAGESIC® patch at doses based on previous opoiod treatment. Titration in all studies was permitted every 72 hours as needed, based on use of rescue medication and pain assessments. Additional pharmacokinetic information was obtained from FEN-FRA-4, a single dose study in eight nonopioid tolerant patients.

As open-label studies, efficacy measures were incorporated only to provide descriptive information and in support of the dosing assessments.

Safety

The safety database consisted of 292 pediatric patients, distributed across the following age ranges: 2 < 6 (n = 66), 6 < 12 (n = 100), 12 < 16 (n = 117), and 16<18 (n=9). One hundred eighty-three patients received DURAGESIC for more than 16 days but fewer than 61 days. The vast majority of the pediatric patients had pain related to an underlying malignancy or its treatment.

None of the 94 deaths was clearly attributable to study drug. Over half of the subjects (57%) experienced at least one serious adverse event (SAE). Of the SAEs that could be attributed to study drug, none was unexpected for a product containing a potent opioid.

The most common adverse events were fever (35%), vomiting (33%) and nausea (23%). Three patients experienced respiratory depression within 96 hours of beginning Duragesic therapy. Two of the patients died, but there was no evidence to suggest a causal relationship between these deaths and the use of study medication. The third patient's decreased respiratory rate resolved after temporary discontinuation of the study drug.

Dosing

One hundred and forty-seven pediatric patients initiated therapy on a 25-µg/h patch. Ninety-four of these patients were receiving at least 90 mg oral morphine equivalents per day and 53 were receiving 45 to 89 mg oral morphine equivalents per day. The method of conversion from prior opioid to DURAGESIC® was well tolerated. Approximately 90% of the total daily opioid requirement (DURAGESIC® plus rescue medication) was provided by DURAGESIC®.

Forty-one percent of patients required dose titration with a mean of 5.6 days until the first dose titration was warranted. Of the 121 patients who received their first titration within the first two weeks, 45% required subsequent dose titration with an average time to subsequent titration of 3.8 days. The titration method, which increased DURAGESIC® by 25 µg/h for each 45 mg of morphine or equivalent opioid taken as rescue medication, was well tolerated.

Pharmacokinetics

The pharmacokinetic data submitted consists of a stand-alone pharmacokinetic study (FEN-FRA-04) and population pharmacokinetic analysis of data obtained from clinical studies FEN-USA-87 and FEN-INT-24.

Study FEN-FRA-04 documented that fentanyl plasma levels for 1.5 - 5 year old surgical patients were approximately twice as high as those for adult surgical patients. According to the population pharmacokinetic analysis, the pharmacokinetic profiles of fentanyl were similar for pediatric and adult patients.

Based on the safety experience obtained from the pediatric clinical trials, the proposed pediatric dosing regimen in the DOSAGE and ADMINISTRATION of the package insert has been recommended.

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Bob Rappaport

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