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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-813

2/23/01

Alza Corporation
P. O. Box 7210
Mountain View, CA 94039-7210

WRITTEN REQUEST

Attention: Eleanor Sims, Ph.D.
Manager, Regulatory Affairs

Dear Dr. Sims:

Reference is made to the Proposed Pediatric Study Request submitted by Janssen Research Foundation on March 19, 1999, and their amendments dated November 30, 1999, and December 15, 2000, for Duragesic (fentanyl transdermal system).

We also refer to your Proposes Pediatric Study Request dated December 15, 2000, where you request appropriate actions be taken to rectify an error by which a previous Written Request as amended was issued to Janssen Research Foundation instead of Alza Corporation, the NDA holder.

To obtain needed pediatric information on this active moiety, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study:

Type of study:
A study of appropriate design to examine safety, dose conversion and titration, and pharmacokinetics of Duragesic in children ≥ 2 years and < 16 years of age.

Objectives/rationale:
- 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, which may be conducted through a population pharmacokinetics approach.

Population:
Children ≥ 2 years and < 16 years of age, evenly distributed across this age range. A minimum of one hundred and fifty patients in total, providing adequate representation in children ≥ 2 years and < 6 years of age.

Study design:
Starting dosage should be calculated based on the subjects total daily dose of opioid analgesic just prior to entering the study. Patients whose total daily dose is equivalent to 30 to 45 mg of morphine should

start with a 12.5 µg/h patch. Dose titration should be based on the total daily amount of rescue medication taken during the three prior days, with 45 mg morphine equivalent resulting in a dose increase by a 12.5 µg/h fentanyl patch and 90 mg morphine equivalent resulting in a dose increase by a 25 µg/h fentanyl patch. The rescue medication may be chosen by the patient, parent, or physician, but may not contain any form of fentanyl. Patients must receive adequate monitoring of respiratory status for the first 3 days of the fentanyl transdermal patch use. This may be accomplished by hospitalization or home apnea/oxygen saturation monitoring. The primary treatment period is 15 days. Four or five blood samples for population pharmacokinetics analysis should be obtained during the 15-day primary treatment period from all subjects.

Entry criteria:
Inclusion: Male and female children with chronic pain of a well-documented etiology requiring around-the-clock administration of opioids, for a minimum of one week prior to enrollment. Patients must have been receiving a minimum total daily opioid dose equivalent to 30 mg of morphine sulfate or more and have a projected need for around-the-clock opioids for at least the length of the primary treatment period.

Exclusion: Skin disease that precludes the use of the transdermal system or that could affect the absorption of fentanyl or local tolerability, Known sensitivity to fentanyl, other opioids, or adhesives. Life expectancy of less than the length of the treatment period (15 days). Patients whose pain is due to surgery.

Clinical assessments:
- Safety: vital signs, adverse experiences, post-treatment physical examination, and other appropriate safety evaluations.
- Therapeutic endpoints: VAS scale to assess pain, use of rescue medication, and/or Global Assessment of Pain treatment scale, and/or Bieri Faces scale, and/or Play Performance Scale, and/or Child Health Questionnaire (CHQ).

Analysis of the data to be performed:
Descriptive analysis of standard pharmacokinetic parameters of fentanyl (including clearance and volume of distribution). Relevant covariates such as age, weight, gender, site of application, dose, concomitant medications, and Tanner stage should be examined in the population pharmacokinetic analysis.

Drug-specific safety concerns:
The fentanyl transdermal system results in the formation of a depot of drug in the skin significantly prolonging functional half life. This could result in prolongation of adverse events such as respiratory depression. As a result, patients respiratory status must be monitored for the first three days as noted in the study design. Patients treated with concomitant medications that inhibit cytochrome P450 3A4 isoenzyme should be carefully monitored.

Statistical information:
Descriptive summaries and tables of the pharmacokinetic parameters, adverse events, and safety data.

Labeling that may result from this study:
Changes to the Clinical Pharmacology, Pediatric Use, and Dosage and Administration sections; and any other sections as appropriate.

Format of reports to be submitted:
Full study report not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. A right of reference should be included for studies conducted by other persons.

Timeframe for submitting reports of the study:
Reports of the above studies must be submitted to the Agency on or before December 1, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as **a supplement to an approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. All requests for changes to this Written Request should be submitted to NDA 19-813 by Alza Corporation and not by Janssen Research Foundation. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely yours,

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research