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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

11/30/00

NDA 17-577
NDA 18-211
NDA 20-897
IND 48,930

ALZA Corporation
Attention: Steve Ketchum, Ph.D.
Senior Director, Regulatory Affairs
1900 Charleston Road P.O. 7210
Mountain View, CA 94039-7210

Dear Dr. Ketchum:

Reference is made to your Proposed Pediatric Study Request submitted on October 6, 2000 for Ditropan XL [redacted] Extended-release Tablets, IND 48,930. We also refer to your facsimile dated November 1, 2000 to IND 48,930.

To obtain needed pediatric information on oxybutynin chloride, 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 two studies and two critical analyses.

Study #1:

Type of study:

Pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]) study

Objectives:

To evaluate the pharmacokinetic profiles of Ditropan (oxybutynin chloride) syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions on stable daily doses of oxybutynin chloride. To evaluate oxybutynin dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish a safe and effective dosage regimen of Ditropan syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple-dose level, minimum 2-week duration, PK and PD study.

For patients receiving oxybutynin chloride, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of 2 weeks of treatment with oxybutynin.

Age group in which study will be performed:

Ages one to five years

Number of patients to be studied:

Enroll approximately 15 patients to have at least eight patients for describing PK/PD profile.

Study endpoints:

Appropriate urodynamic evaluation: this may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions.
PK: Appropriate stereospecific analysis of drug and metabolite plasma profiles, the sampling should be adequate to characterize the complete PK profile in this age group
Dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)
Safety: Appropriate monitoring of adverse events, urodynamic, cardiovascular and laboratory parameters
Safety: Number of patients terminated prematurely

Drug information:

The drug product to be used in this study is the following commercially available formulation: Ditropan (oxybutynin chloride) Syrup, 5 mg/5 mL. A total daily dose of 5–15 mg will be administered orally divided into two or three doses.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

PK: Descriptive stereospecific analysis to include reporting of AUC, C_{max}, and C_{min} for drug and metabolite.
Urodynamic: Urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.
Safety: Safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

Report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to 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.

Study #2:

Type of study:

Safety and dose-response study

Objectives:

To document the safety and tolerability of Ditropan (oxybutynin chloride) Syrup, Ditropan (oxybutynin chloride) Tablets, and/or Ditropan XL (oxybutynin chloride) extended-release tablets in pediatric patients with detrusor hyperreflexia due to neurogenic conditions on stable daily doses of oxybutynin chloride.
To evaluate oxybutynin dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish safe and effective oxybutynin dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

24-week, open label, multiple-dose level, safety, dose response study. There will be a PK/PD substudy.

For patients receiving oxybutynin chloride, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated at the Week 12 Visit. For patients who withdraw prior to Week 12 Visit, an attempt will be made to repeat urodynamic evaluation while patient is still on the study dose of oxybutynin and before patient withdrawal.

Age group in which study will be performed:

Ages six to fifteen years

Number of patients to be studied:

Enroll approximately 140 patients with approximately equal numbers of patients between the six to ten and eleven to fifteen age groups, to ensure a total of approximately 50 patients finishing 24 weeks of treatment with oxybutynin. The PK subgroup will include a minimum of 32 patients with approximately 8 patients and a minimum of 5 patients on the syrup formulation, approximately 8 patients and a minimum of 5 patients on the tablet formulation, and approximately 8 patients and a minimum of 5 patients on the extended release formulation.

Study endpoints:

Primary endpoint: volume of void. *Other endpoints:* appropriate urodynamic evaluations, which may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and presence of uninhibited detrusor contractions. In addition, we are requesting an assessment of occurrence of accidents/leakage episodes.
PK: Appropriate stereospecific analysis of drug and metabolite plasma profiles; the sampling should be adequate to characterize the complete PK profile in this age group
Dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)
Safety: Appropriate monitoring of adverse events, urodynamic, cardiovascular and laboratory parameters
Safety: Number of patients terminated prematurely

Drug information:

The drug products to be used in this study are the following commercially available formulations: Ditropan (oxybutynin chloride) Syrup, 5 mg/5 mL; Ditropan (oxybutynin chloride) Tablets, 5 mg; or DitropanXL (oxybutynin chloride) Tablets, 10 mg and 15 mg.

For Ditropan (oxybutynin chloride) Syrup 5 mg/5 mL and for Ditropan (oxybutynin chloride) Tablets 5 mg, a total daily dose of 10 mg or 15 mg will be administered orally divided into two or three doses. For DitropanXL (oxybutynin chloride) Tablets 10 mg and 15 mg, a total daily dose of 10 mg or 15 mg will be administered orally in one dose.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents (e.g. constipation, dry mouth). Patients unable to swallow the DitropanXL Tablets whole should be placed on Ditropan Syrup or Ditropan Tablets because chewing, dividing, or crushing the Ditropan XL Tablets could be unsafe.

Statistical information:

PK: For each of the two age subgroups, for each of the two dose levels (10 and 15 mg), and for each dosage form, descriptive stereospecific analysis are to be performed to include reporting of AUC, C_{max}, and C_{min} for drug and metabolite.

Urodynamic: Urodynamic measurements are to be tabulated and contrasted from baseline to end of study, and the measurements will be categorized and grouped according to total daily dose, dosage form, and age subgroup. Changes in void volume over time are to be described in a similar manner.

Safety: Safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

Report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to 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.

Critical Analyses:

Provide a critical analysis of urodynamic data in adults with detrusor hyperreflexia due to neurogenic conditions treated with oxybutynin chloride. This will be submitted with the final study reports. The analysis will review clinical trial data and the published literature and will describe the dose-effect (urodynamic) of oxybutynin.

Provide a critical analysis of oxybutynin usage in pediatric patients with emphasis on its safety profile, PK, PD, and efficacy. This will be submitted with the final study reports.

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 new drug application or as a supplement to your 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. 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 Evelyn R. Farinas, R. Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Victor Raczkowski, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research