DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 21-287

sanofi-aventis U.S. LLC
Attention: Linda Gambone, Ph.D.
Assistant Director, Drug Regulatory Affairs
9 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Gambone:

Reference is made to your July 14, 2005, Proposed Pediatric Study Request submitted to NDA 21-287 for Uroxatral® (alfuzosin hydrochloride).

To obtain needed pediatric information on alfuzosin hydrochloride, 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 studies:

Types of studies:

Study 1: A 4-week, open-label, randomized, multiple-dose, parallel-dose group pharmacokinetic and safety study in pediatric patients, age 2-16 years, with elevated detrusor leak point pressure (LPP) (≥ 40 cm H_2O) of neurologic origin. Pharmacodynamic measurement (LPP) should be performed in all patients at baseline and in those patients who complete the 4-week study.

Study 2: A 12-week, double-blind, randomized, placebo-controlled, parallel-dose, efficacy, pharmacodynamic and safety study comparing two doses of alfuzosin followed by a 40-week (10-month) open-label extension phase in pediatric patients, age 2-16 years, with elevated detrusor LPP (≥ 40 cm H_20) of neurologic origin. Population pharmacokinetics will be investigated at 12 weeks.

Study 3: A 12-week, open-label, non-comparative pharmacodynamic and safety study in pediatric patients, age 2-16 years, with grade 1 or 2 hydronephrosis associated with elevated detrusor LPP (≥ 40 cm H_20) of neurologic origin followed by a 40-week (10-month) extension phase. Population pharmacokinetics will be investigated at 12 weeks.

Study objectives:

Study 1:

- To characterize the pharmacokinetics (PK) of two doses of alfuzosin (0.1 mg/kg/day; 0.2 mg/kg/day) given as a solution containing 0.2 mg/mL of alfuzosin or tablets containing alfuzosin 1.5 mg in children and adolescents 2 - 16 years of age

with elevated detrusor LPP of neurologic etiology stratified into two age groups (2 - 7 years and 8 - 16 years);
- To investigate the safety and tolerability of the two doses of alfuzosin in children and adolescents;
- To evaluate the effect of two doses of alfuzosin on detrusor LPP in children and adolescents.

Study 2:
- To evaluate the efficacy of alfuzosin in comparison to placebo on the detrusor LPP in children and adolescents 2 – 16 years of age with elevated detrusor LPP (≥ 40 cm H_2O) of neurologic etiology;
- To investigate the safety and tolerability of two doses of alfuzosin in comparison to placebo in children and adolescents;
- To evaluate the effects of the two doses of alfuzosin in comparison to placebo on detrusor compliance and urinary tract infection;
- To investigate the population pharmacokinetics of alfuzosin;
- To evaluate the 12-month long-term safety of alfuzosin 0.1 mg/kg/day and 0.2 mg/kg/day.

Study 3:
- To determine the efficacy of alfuzosin in the treatment of children and adolescents 2 - 16 years of age with newly diagnosed or progressive hydronephrosis due to neuropathic bladder dysfunction;
- To investigate the safety and tolerability of alfuzosin 0.2 mg/kg/day in children and adolescents;
- To investigate the number of UTI episodes;
- To investigate the population pharmacokinetics of alfuzosin.

Indication:

The treatment of pediatric patients, age 2 to 16 years, with elevated detrusor leak point pressure associated with a known neurological disorder (e.g., spina bifida).

Study populations, including sample sizes:

Study 1: Pediatric patients, age-stratified into two groups (2-7 and 8-16 years), with elevated detrusor LPP ≥ 40 cm H_2O associated with a known neurologic disorder should be enrolled. For PK characterization, randomize an adequate number of patients in order to obtain approximately 6 patients with evaluable pharmacokinetic information at each dose level within each age group.

Study 2: Enroll approximately 150 pediatric patients, with elevated detrusor LPP ≥ 40 cm H_2O associated with a known neurologic disorder (stratified by age, 2-7 and 8-16 years, and by current use of anticholinergic medication) to ensure that approximately 75 and 50 patients receive alfuzosin for at least 6 months and 1 year, respectively. At least 25% of completers should be in the 8-16 age group.

Study 3: Enroll approximately 20 pediatric patients, age 2-16 years, with a known neurologic disorder, detrusor LPP ≥ 40 cm H_20 and grade 1 or 2 hydronephrosis.

Study designs:

Study 1: An open-label, pharmacokinetic study: Study patients should be stratified into two age groups (age 2-7 years and 8-16 years)**,** and then randomized to one of two dose groups: 0.1 mg/kg/day or 0.2 mg/kg/day. Pharmacokinetic data should be obtained on Day 1 and at steady-state. Pharmacodynamic measurement (LPP) should be assessed at baseline and in those patients completing the study at Week 4. Safety and tolerability should also be assessed.

Submit safety and pharmacokinetic results to the Agency and receive feedback from the Agency prior to the initiation of the primary efficacy studies (Study 2 and Study 3).

Study 2: A randomized, double-blind, placebo-controlled study: Study patients with LPP ≥ 40 cm H_2O should be stratified by age (2-7 years and 8-16 years) and by current use of anticholinergic medication. Patients should be randomized into one of four treatment groups: 1) alfuzosin 0.1 mg/kg/day, 2) placebo 0.1 mg/kg/day, 3) alfuzosin 0.2 mg/kg/day, or 4) placebo 0.2 mg/kg/day. Patients should receive alfuzosin or placebo in a 2:1 ratio. LPP should be assessed at baseline and at Week 12. For the 40-week extension phase, patients on active treatment should continue the same treatment including dose. Patients on placebo should remain in their dose group but should be converted to alfuzosin treatment.

Study 3: An open-label, 12-week study followed by a 40-week (10-month) extension phase: For study entry, patients must have LPP ≥ 40 cm H_2O and have grade 1 or 2 hydronephrosis of neurologic etiology. One dose of alfuzosin should be investigated, 0.2 mg/kg/day. Hydronephrosis, assessed using renal ultrasound, should be performed at baseline and at Weeks 12 and 52.

Study Endpoints:

PK and efficacy endpoints

Study 1: The pharmacokinetic endpoints should include C_{min}, C_{max}, t_{max}, AUC and accumulation (R_{ac}) at steady-state. The parameters C_{max}, t_{max}, and AUC should also be characterized following the first dose. Pharmacodynamic assessment of LPP should be obtained at baseline and at Week 4 in those patients who complete the study. PK/PD relationship for safety and efficacy should be explored and data included in the sNDA.

Study 2: The primary efficacy endpoint should be the proportion of patients with detrusor LPP <40 cm H_2O at Week 12. The secondary endpoints should include relative change in detrusor LPP, relative change in detrusor compliance, and number of UTI episodes during the treatment period compared to placebo. Population pharmacokinetics and the effects of covariates, including age, body weight, gender, and concomitant medications on alfuzosin pharmacokinetics should be explored. Exposure-response relationship

should also be explored. These data should be presented in conjunction with the exposure-response information derived from study 1.

Study 3: The primary efficacy endpoint should be change in grade of hydronephrosis at Week 12 compared to baseline. The secondary endpoint should include the number of UTI episodes. Population pharmacokinetics should be explored.

Analysis and presentation of PK and efficacy endpoints

Study 1: Information derived from this study should be used to characterize pharmacokinetics and safety of alfuzosin in the target pediatric population. Analysis of PK parameters, such as C_{min}, C_{max}, T_{max}, AUC and R_{ac}, should be presented using descriptive summary statistics. The effect of body weight and gender on PK parameters should be explored. Data derived from the exploratory exposure-response analysis should be included in the sNDA.

Study 2: The trial should compare each dose of alfuzosin (0.1 mg/kg/day and 0.2 mg/kg/day) to placebo for the primary endpoint, proportion of patients with detrusor LPP <40 cm H_20 at Week 12. Each dose of alfuzosin should be compared to placebo using a two-sided Fisher's exact test at the 0.05 significance level and adjusting for multiple comparisons.

Secondary endpoints should also be compared between active and placebo treatments and should include relative change in detrusor LPP, relative change in detrusor compliance, and number of UTI episodes during the treatment period. Appropriate methods of analysis should be applied.

Results for the primary and secondary endpoints should also be presented by age and by anticholinergic use.

A separate subgroup analysis to evaluate small changes in LPP around 40 cm H_2O should also be submitted. The analysis should include all patients whose post-treatment LPP fell below 40 cm H_2O with a baseline LPP between 41-45 cm H_2O.

ECG data should also include a separate analysis of QT prolongation including outliers.

Study 3: This study should be considered exploratory to investigate whether alfuzosin can decrease hydronephrosis. The primary efficacy variable is based on a responder analysis where positive response represents a hydronephrosis grade change from baseline to endpoint of ≥ 1. The response rate should be calculated along with its two-sided 95% confidence interval. Descriptive statistics for efficacy and safety should be presented.

Drug information:

- **Route of administration:** Oral
- **Formulation:** Use an age-appropriate formulation in the studies described above.
  If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will

seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable, age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- **Regimen:** The proposed alfuzosin solution (0.2 mg/mL) should be administered three times daily with a dosing interval of at least 4 hours. The proposed alfuzosin 1.5 mg tablets should be administered twice daily with a dosing interval of approximately 12 hours.
- **Doses:** 0.1 mg/kg/day and 0.2 mg/kg/day. All doses should be weight-adjusted.

Statistical information, including power of study and statistical assessments

Study 1 The statistical analyses should be descriptive.

Study 2 This study should be considered a superiority trial aimed at demonstrating superiority of alfuzosin over placebo for at least one alfuzosin dose. The study should have 95% power to detect a significant difference at the two-sided 0.025 alpha level. The model used to analyze the primary endpoint should include the stratification factors of age and use/non-use of anticholingeric medication.

Study 3: The statistical analyses should be descriptive.

Drug specific safety concerns and evaluations:

Safety should be assessed at baseline and periodically as per protocol in all three studies by assessments to include:

- Soliciting reports of clinical adverse events
- Physical examination, including supine/seated blood pressure and pulse rate

- Laboratory evaluations of clinical chemistry (including LFTs), hematology and hormonal parameters (T3, T4, estradiol, LH, FSH, prolactin and testosterone [total and free]) at baseline and approximately every three to five months
- Tanner staging
- Vision testing using a visual eye chart
- Cognition testing measured by the modified Epworth Sleepiness Scale
- Electrocardiograms
- Renal ultrasound (applicable to Study 3)

All protocols must specify individual patient study discontinuation criteria. Studies 2 and 3 must include the utilization of a data safety monitoring board with pre-specified stopping rules.

Safety concerns specific to the use of alpha$_1$-blockers that should be conveyed in the parent/guardian consent form include:

- Risk of dizziness, syncope and fatigue: Patients and parents/caretakers should be instructed to watch for possible occurrence of these adverse events.
- A juvenile rat study showed hormonal changes in thyroid function, testosterone and estrogen levels.
- In controlled clinical studies in adults, alfuzosin caused a small change in the QT interval.
- Mammary gland fibroadenoma and adencarcinomas have been observed in female mice treated with other alpha$_1$-blockers, not including alfuzosin.

All safety data collected should be evaluated with descriptive statistics. For Study 2, active treatment should be compared to placebo for all safety assessments.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request should be submitted with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before April 30, 2011. The 6- and 12-month safety data must be submitted at the time of the sNDA submission and not as a 4-month safety update.

Please keep in mind 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.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. 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 (NDA) 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, 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.

As a reminder, you are responsible for compliance with section 113 of the Food and Drug Administration Modernization Act of 1997 and section 15 of the Best Pharmaceuticals for Children Act of 2002 by registering certain clinical trials in the Clinical Trials Data Bank (http://clinicaltrials.gov/). If your drug is for the treatment of a serious or life-threatening disease or

condition and you are conducting trials to test its effectiveness, then you must register the trials. Although not required, we encourage you to register trials for non-serious diseases. For additional information on registering your clinical trials, including the required and optional data elements, refer to the Protocol Registration System (PRS) Information Site (http://prsinfo.clinicaltrials.gov) and FDA's Guidances for Industry entitled "*Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*" (March 2002; revised draft January 2004).

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 796-0928.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz

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