DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 2

NDA 21-287

sanofi-aventis U.S. LLC
Attention: Linda Gambone, Ph.D.
Assistant Director, Drug Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Gambone:

Please refer to your correspondence dated June 6, 2008, requesting changes to FDA's February 21, 2006, Written Request for pediatric studies for Uroxatral® (alfuzosin HCl extended release tablets).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. Deleted words are indicated by strikethrough and inserted words are underlined. All other terms stated in our Written Request issued on February 21, 2006, and as amended on June 15, 2006, remain the same.

Under **Types of studies:**

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, or 3 hydronephrosis associated with elevated detrusor LPP ($\geq$ 40 cm H_20) of neurologic origin followed by a 40-week (10-month) extension phase. Population pharmacokinetics will be investigated at 12 weeks.

Under **Study populations, including sample sizes:**

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

Under **Study designs:**

Study 3: An open-label, 12-week study followed by a 40-week (10-month) extension phase: For study entry, patients must have LPP $\geq$ 40 cm H_2O and have grade 1, ~~or~~ 2, or 3 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. For patients with grade 3 hydronephrosis, additional ultrasounds will be performed at 26 and 38 weeks.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated February 21, 2006, as amended by this letter and previous amendment(s) dated June 15, 2006, must be submitted to the Agency on or before June 16, 2010, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-827-5911) 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Uroxatral® (alfuzosin HCl extended release tablets) is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval or complete response); or
4. the exclusivity determination (i.e., granted or denied).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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 to the pediatric population.

If you have any questions, call Olga Salis, Regulatory Project Manager, at (301) 796-0837.

Sincerely,

{See appended electronic signature page}

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

Attachment (Complete Copy of Written Request as amended)

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 H2O) 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 H20) 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, 2, or 3 hydronephrosis associated with elevated detrusor LPP (≥ 40 cm H20) 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, 2, or 3 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, 2, or 3 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. For patients with grade 3 hydronephrosis, additional ultrasounds will be performed at 26 and 38 weeks.

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 stepby-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 June 16, 2010. 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.

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

10/17/2008 10:35:09 AM