DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 20-579

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Brill:

To obtain needed pediatric information on tamsulosin 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 combined pharmacokinetic/pharmacodynamic (PK/PD) characterization and long-term, open-label safety study of tamsulosin hydrochloride in pediatric patients 2 years – 16 years of age with elevated detrusor leak point pressure (LPP) associated with a known neurological disorder (e.g. spina bifida). The PK/PD characterization is to be performed as a lead-in to a long-term (12-month) safety evaluation of tamsulosin in this specific population.

Study 2: A randomized, double-blind, placebo-controlled, 14-week, safety and efficacy study in pediatric patients 2 years – 16 years of age with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida).

Study objectives:

Study 1: To characterize tamsulosin systemic exposure and pharmacokinetic/pharmacodynamic profile following weight range-based dosing of tamsulosin HCl at three dose levels and to evaluate the long-term safety, tolerability and maintenance of efficacy of tamsulosin hydrochloride as treatment in pediatric patients 2 years – 16 years of age with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida).

Study 2: To evaluate the efficacy of tamsulosin hydrochloride over a range of doses, for the primary endpoint, percentage of patients who achieve reduction of LPP below 40 cm H_2O, in pediatric patients 2 years – 16 years of age with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida).

To determine the safety and tolerability of a range of dose levels of tamsulosin hydrochloride as treatment in pediatric patients 2 years – 16 years of age with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida).

To characterize the population pharmacokinetics of tamsulosin in the target population using a sparse sampling strategy.

Indication:

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

Study populations, including sample sizes:

Study 1: For the PK/PD characterization, randomize approximately 27 patients, so that there are approximately 9 patients with PK/PD information for each dose level (low, medium and high) and for each body weight category (i.e. 12.1- 25 kg, 25.1-50 kg, and 50.1-100 kg). Enroll sufficient numbers of patients across all age ranges.

For the long-term safety characterization, enroll a sufficient number of pediatric patients 2 years – 16 years of age with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida) to ensure that approximately 75 and 50 patients receive tamsulosin hydrochloride for at least 6 months and 1 year, respectively.

Study 2: Enroll a sufficient number of patients to ensure that approximately 120 pediatric patients 2 years – 16 years of age with elevated detrusor LPP associated with a known neurological disorder (e.g. spina bifida) complete the study, with approximately 30 patients in each dose group (low, medium and high). Enroll sufficient numbers of patients of each age category (2-<5 years, 5-<10 years, and 10-16 years) and body weight categories (12.1 - 25 kg, 25.1 - 50 kg, and 50.1 - 100 kg) to allow for evaluation of consistency of effects.

Study designs:

Study 1: An open-label study divided into a PK/PD characterization portion, followed by a long-term safety and tolerability portion. The PK/PD portion should include approximately 27 patients who are randomized to low, medium and high doses. This randomization should be stratified by weight (12.1 - 25 kg, 25.1 - 50 kg, and 50.1 - 100 kg). Day 1 pharmacokinetics should be characterized at the low dose in all patients and tamsulosin steady-state pharmacokinetics should be assessed in all patients when they finish 2 weeks of treatment on their final randomized dose level (i.e. on Day 14, 21 and 28 for the low, medium and high dose groups, respectively). When the PK portion of the trial is completed, the PK/PD and safety information should be shared with the Agency for our review. In addition, a comparison of the target pediatric exposure data against existing adult data should be provided in this report. Except for the first 27 patients who may continue in the study, no additional patients will be treated until the Agency has formally agreed that it is acceptable to do so. The sponsor must receive a formal statement from the Agency that patients who did not participate in the PK/PD portion of

the study may begin treatment, increasing doses according to the individual's efficacious dose level.

Study 2: A randomized, double-blind, placebo-controlled, safety and efficacy study. The randomization to placebo, low, medium or high dose groups should be stratified by: location of study centre (North America or Europe), age group (2-<5 years, 5-<10 years, and 10-16 years), and concomitant use of anti-cholinergic medication. The study should have a dose-titration lead-in phase and a 12-week maintenance phase. This study may not be initiated until the preliminary PK/PD and safety information from approximately 27 patients from Study 1 have been assessed by the Agency, and the sponsor has been informed that it is acceptable to continue Study 1 and to initiate Study 2.

Study endpoints:

PK and efficacy endpoints:

Study 1: The pharmacokinetic endpoints should be C_{max}, t_{max}, AUC, and $t_{1/2}$ at steady state. The parameters C_{max} and t_{max}, should also be characterized after the first dose. For efficacy, the primary endpoint should be the percentage of patients who achieve a leak point pressure (LPP) less than 40 cm H_2O based upon two out of three evaluations. The secondary efficacy endpoints should be: the percentage of patients who maintain their detrusor leak point pressure (LPP) below 40 cm H_2O during the study, and the percentage of patients in whom hydronephrosis and/or hydroureter improves or stabilizes on renal ultrasound.

Study 2: The primary efficacy endpoint should be the percentage of patients who decrease their detrusor leak point pressure (LPP) to less than 40 cm H_2O based upon by two out of three maximum evaluations at the end of the maintenance treatment phase (end-of-study). The secondary efficacy endpoints should be: improvement of functional bladder capacity, percent change in detrusor leak point pressure from baseline, change in volumes obtained by catheterization as obtained from diaries, and improvement or stabilization of hydronephrosis and/or hydroureter on renal ultrasound.

Also, characterize the systemic tamsulosin exposures and explore the effects of covariates including age, gender, body weight, AAG on the resultant PK.

Analysis and presentation of PK and efficacy endpoints:

Study 1: Information derived from the PK/PD portion of this study should be used to characterize tamsulosin pharmacokinetics and exposure-response relationship in the target pediatric population. Resultant exposures in the target population should be compared with that of existing adult and pediatric data. Analysis of the PK parameters, such as C_{max}, t_{max}, AUC and $t_{1/2}$, should be presented using descriptive summary statistics. Dose proportionality should be explored using a model that describes the relationship between dose per kilogram body weight and the PK endpoints. The effect

of covariates of interest including body weight, gender, age, AAG on PK parameters should be explored.

Explore the possible association of pharmacokinetics with pharmacodynamic parameters.

Study 2: Treatment with tamsulosin hydrochloride should be compared to placebo for the primary efficacy endpoint, percentage of patients who achieve a detrusor LPP less than 40 cm H_2O based upon two out of three evaluations, at the end of the maintenance treatment phase. Secondary efficacy endpoints should also be compared between active and placebo treatments and should include: improvement of functional bladder capacity on urodynamic study, percent change in detrusor LPP from baseline to end of study, change in volumes obtained by bladder catheterization as obtained from diaries, and improvement or stabilization of hydronephrosis and/or hydroureter on renal ultrasound.

The primary efficacy endpoint should be analyzed using a logistic regression model with the dependent variable being dichotomous: the achievement versus non-achievement of a successful response, defined as a detrusor LPP less than 40 cm H_2O on two out of three evaluations at the end of the maintenance treatment phase. The model should include three independent variables used in stratification of the randomization: location of study centre (North America or Europe), age group (2-<5 years, 5-<10 years, and 10-16 years), and concomitant use of anti-cholinergic medication, as well as a treatment variable.

Perform these analyses using all patients who are randomized, who receive at least one dose of randomized treatment and who have at least one on-treatment evaluation of the primary endpoint.

Drug information:

- **Route of administration:** oral
- **Formulation:** Use an age-appropriate formulation in the study(ies) 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:** Once daily - 30 minutes after the same meal.

- **Doses:**
  - For children weighing 9.0-12 kg: 0.025 mg and 0.05 mg.
  - For children weighing 12.1-25 kg: 0.025 mg, 0.05 mg, and 0.1 mg.
  - For children weighing 25.1-50 kg: 0.05 mg, 0.1 mg, and 0.2 mg.
  - For children weighing more than 50kg: 0.1 mg, 0.2 mg, and 0.4 mg.

Safety concerns and evaluations:

Safety should be assessed in both studies by periodic assessments to include:
- Soliciting reports of clinical adverse events
- Laboratory evaluations of clinical chemistry and hematology, including endocrinology parameters (prolactin, estradiol, testosterone, LH, FSH, and T3/T4)
- Urinalysis
- Physical examinations, including supine and sitting blood pressure and pulse rate
- Electrocardiograms
- Vision testing
- Cognitive testing
- Urodynamics, including post-void residual
- Renal ultrasound

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

Safety concerns specific to the use of alpha-1 blockers in the adult male population include first-dose syncope, postural hypotension, and dizziness. Other reported adverse events in controlled trials include: headache, nasal stuffiness, impaired ejaculation, fatigue, somnolence, diarrhea, and blurred vision. In the post-marketing period, the following additional adverse events have been reported: allergic-type reactions including angioedema, priapism, palpitations, constipation, vomiting, and skin desquamation.

In nonclinical studies, an increased incidence of mammary gland fibroadenomas and adenocarcinomas was observed in female mice and is believed to be secondary to drug-induced hyperprolactinemia. It is not known if alpha-1 blockers elevate serum prolactin in humans. The relevance of prolactin-mediated mammary tumors in mice to human risk is not known.

Assure that this information is conveyed in the parent/guardian consent form.

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 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 July 1, 2009. 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 of 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.
Deputy 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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