U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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|---|---|
| **NDA/Serial Number:** | 20-579 / SE8-026 |
| **Drug Name:** | Flomax® (tamsulosin HCl) Capsules 0.4 mg |
| **Indication(s):** | Treatment of the signs and symptoms of Benign Prostatic Hyperplasia |
| **Applicant:** | Boehringer Ingelheim Pharmaceuticals, Inc. |
| **Date(s):** | Submission Date: 6/26/2009 |
| | PDUFA Due Date: 11/26/2009 |
| **Review Priority:** | Priority |
| **Biometrics Division:** | Division of Biometrics III |
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**Keywords:** NDA review, clinical studies

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

The results show that there is no therapeutic value of tamsulosin HCl for the decrease of detrusor leak point pressure (LPP) in pediatric patients with known neurological deficit.

From a statistical perspective, although there is no statistically significant difference in efficacy between Tamsulosin HCl and placebo treated pediatric patients with neuropathic bladder, this submission fulfills the Pediatric Written Request (PWR).

## 1.2 Background

Tamsulosin hydrochloride (HCl) has been developed as a modified-release capsule for the treatment of benign prostatic hyperplasia (BPH) in adults and was approved in the US for this indication under NDA 20-579 in 1997. Tamsulosin HCl is available as Flomax® 0.4 mg capsules.

This efficacy supplement was submitted to support the changes to the Flomax labeling regarding use in pediatric patients to fulfill the PWR issued by FDA on January 10, 2006 and to determine the exclusivity extension.

## 1.3 Statistical Issues and Findings

There was no statistical issue in this submission. However, the sponsor noted two minor data discrepancies after the database was locked and submitted in the submission. These discrepancies were resolved by the sponsor and did not have any impact on the overall integrity of the study.

This reviewer confirms that there was no statistical and clinically significant difference between tamsulosin HCl dose groups and placebo group for all primary and secondary endpoints. The child's age group, weight and use of anticholinergic medication at baseline were not associated with LPP response rates. No dose response trend was observed. However, the LLP response rate was significantly lower in the Asian patients compared to patients in other regions.

# 2. INTRODUCTION

## 2.1 Overview

Flomax® was approved in 1997 for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The Applicant has submitted one pivotal, Phase 3 study (Study 527.51) to support the changes to the Flomax labeling regarding use in pediatric patients in order to determine the exclusivity extension. Table 1 presents a brief summary of this study.

**Table 1: Brief Summary of Clinical Study for Flomax® (tamsulosin HCl)**

| Study Number (No. of Sites / Country) Dates of Study Conduct | Subject Population | Primary Endpoints | Treatments | Number Randomized (ITT) | Design[1] |
|---|---|---|---|---|---|
| 527.51 (8/ U.S. & 12/ Europe & 20/ Asia) Jan. 2008 to Feb. 2009 | Chidren between two and 16 years of age with elevated detrusor leak point presure associated with a known neurologic deficit. | Response to treatment defined as patients who decreased their detrusor leak point pressure (LPP) at week 14. | Placebo | 41 (41) | R, DB, PC, MC, DR |
| | | | Tamsulosin Low | 40 (40) | |
| | | | Tamsulosin Medium | 40 (39) | |
| | | | Tamsulosin High | 41 (41) | |
| | | | **Total** | **162 (161)** | |

[1] R = Randomized, MC = Multicenter, DB = Double-blind, PC = Placebo Control, DR = Dose Ranging

This was a randomized, multicenter, double-blind, placebo-controlled dose ranging study to evaluate the efficacy of tamsulosin hydrochloride (low, medium and high dose) in decreasing the LPP in children with neuropathic bladder at week 14 of treatment. A total of 162 pediatric patients 2 years or older with elevated detrusor leak point pressure associated with a known neurologic deficit were enrolled at 20 study centers in North America, Europe, and Asia. The patient population was stratified by age (2-<5 years, 5-<10 years and 10-16 years) and concomitant use of anti-cholinergic medication.

## 2.2 Data Sources

The study reports and additional information for this submission were available in paper format. The SAS data sets for the study were complete and well documented. These items were located in the Electronic Document Room at \\Fdswa150\nonectd\N20579\N_000 under submission date 6/25/2009.

# 3. STATISTICAL EVALUATION

## 3.1 Design of Study 527.51

Study 527.51 was a multi-national, multicenter, double-blind, randomized, dose-ranging, placebo-controlled trial. The randomization was stratified by age group (2-<5 years, 5-< 1 0 years and 10-16 years of age) and concomitant use of anti-cholinergic medication. Eligible patients were randomized one of four treatment groups: placebo, low, medium or high dose tamsulosin hydrochloride. The clinical trial consisted of two study periods:

- Study Period I: double-blind, dose titration period of 2 weeks
- Study Period II: a double-blind maintenance treatment period of 3 months

The primary efficacy assessment was based on detrusor leak point pressure (LPP) measured by $H_2O$ using a standard urodynamic technique, a cystometrogram. Urodynamic testing was performed at least two times during the scheduled visit to determine consistent results (e.g., 2 LPP < 40cm $H_2O$ or 2 LPP ≥ 40cm $H_2O$). A third test was performed if the results from the first two tests were inconsistent. Urodynamic testing was performed at Visit 1 (screening) and at Visit 7 / Week 14 (end of treatment). The primary endpoint is the response rate at week 14 defined as patient with two LPP measurements < 40cm $H_2O$ based on two confirmatory values at the same visit, or a patient with only 1 LPP measurement and the measurement is < 40cm $H_2O$.

The primary statistical analysis was conducted using logistic regression model with treatment and three covariates: age group, concomitant use of anti-cholinergic medication and geographic region. A test of trend for primary endpoint across the four treatment groups was performed using the Cochran-Armitage test. The Hochberg methodology was used in order to control type I error for multiple comparisons between tamsulosin HCl dose groups and the placebo group.

In addition, the following secondary endpoints were also evaluated:

1) Percent change from baseline in detrusor leak point pressure
2) Change from baseline in actual detrusor leak point pressure
3) Response with regard to hydronephrosis was defined as improvement or stabilization based upon the ultrasound grading at the end of treatment compared to baseline
4) Response with regard to hydroureter was defined as improvement or stabilization based upon a change in the presence or absence of hydroureter at end of treatment compared to baseline
5) Change in baseline urine volumes obtained by catheterisation as recorded in catheterisation diary
6) Change from baseline in number of times patient was wet at time of catheterisation as recorded in catheterisation diary

The same logistic regression analysis was also performed for all the dichotomous secondary efficacy variables. Quantitative endpoints were analyzed using an analysis of covariance model with age group, concomitant anti-cholinergic medication use and treatment group as the independent variables and the baseline values as the covariates.

## 3.2 Results

### 3.2.1 Subject Disposition and Baseline Characteristics

A total of 231 patients were screened, of which 162 patients met eligibility criteria and were randomized. Of these, 161 received at least one dose of study drug. Only one patient in HCl medium dose never received study drug due to withdrawal of consent prior to receiving treatment. Of the 161 patients who received at least one dose of study treatment, 148 (91.9%) patients completed the 14-week treatment regimen. The most common reason for discontinuation prior to 14-week was lost to follow-up. The summary of analysis datasets are summarized in Table 2.

**Table 2: Patient disposition and trial medication completion by treatment group**

| | | Tamsulosin Dose Groups | | | |
|---|---|---|---|---|---|
| | Placebo | Low | Medium | High | Total |
| Enrolled | | | | | 231 |
| Randomised | | | | | 162* |
| Not treated | 0 | 0 | 1 | 0 | 1 |
| Treated, N | 41 | 40 | 39 | 41 | 161 |
| Did not prematurely discont. trial med. N (%) | 36 (87.8) | 36 (90.0) | 36 (92.3) | 40 (97.6) | 148 (91.9) |
| Prematurely discontinued from trial med. N (%) | 5 (12.2) | 4 (10.0) | 3 ( 7.7) | 1 ( 2.4) | 13 ( 8.1) |
| AE (unexpected worsening of disease under study) | 0 | 0 | 0 | 0 | 0 |
| AE (unexpected worsening of pre-existing disease) | 0 | 0 | 0 | 0 | 0 |
| AE other | 1 ( 2.4) | 2 ( 5.0) | 0 | 0 | 3 ( 1.9) |
| Non compl. protocol | 0 | 0 | 2 ( 5.1) | 0 | 2 ( 1.2) |
| Lost to follow-up | 2 ( 4.9) | 2 ( 5.0) | 1 ( 2.6) | 0 | 5 ( 3.1) |
| Consent withdrawn, not due to AE | 1 ( 2.4) | 0 | 0 | 1 ( 2.4) | 2 ( 1.2) |
| Other | 1 ( 2.4) | 0 | 0 | 0 | 1 ( 0.6) |

* Patient 5007 was randomized to medium dose tamsulosin HCl, but withdrew consent prior to receiving treatment.
(Source: Study Report 527.51 Final Report U09-3267-01; Table 10.1.1, page 75)

For treated patients, demographic and baseline characteristics for all treatment groups were similar with respect to age (mean age of 8.2 years), gender (60.2% male) and race (55.3% Asian, 27.3% Caucasian). There were 30 patients in the 2 to 5 years old age group, 70 patients in the 5 to 10 years old age group and 61 patients in 10 to 16 years old age group. A total of 59.6% patients were in the lowest weight group (12.5 to 0025.1 kg), with 31.7% patients in the 25.1 to

50.1 kg and 8.7% in the 50.1 to 100 kg weight groups. A total of 39.1 % of patients were receiving anti-cholinergic medication at baseline.

### 3.2.2 Analysis Datasets

The analyses populations included Treated set (TS), defined as all patients who were documented to have taken at least one dose of randomized treatment.

The Full analysis set-LPP (FAS-LPP): Included all patients in the treated set who received at least one dose of randomized treatment. The FAS-LPP set was used for analysis of the primary endpoint.

The Per protocol set-LPP (PPS-LPP): Included all patients in the FAS-LPP who did not have an important protocol violation related to efficacy.

The numbers of patients for these analysis datasets are summarized in Table 3. There were 23 patients with important efficacy-related protocol violations who were not included in PPS-LPP. The primary efficacy population was the Full analysis set-LPP (FAS-LPP).

**Table 3: Number of patients in analysis sets**

| | | Tamsulosin Dose Groups | | | |
|---|---|---|---|---|---|
| **Patient Analysis Sets** | **Placebo** | **Low** | **Medium** | **High** | **Total** |
| Entered/Randomised, N | 41 | 40 | 40 | 41 | 162* |
| Treated set (TS), N | 41 | 40 | 39 | 41 | 161* |
| Full analysis set (FAS-LPP), N | 41 | 40 | 39 | 41 | 161 |
| FAS-LPP at Week 14 | 34 | 35 | 33 | 33 | 135 |
| Per protocol set (PPS-LPP), N | 37 | 33 | 35 | 33 | 138 |
| PPS-LPP at Week 14 | 30 | 28 | 30 | 27 | 115 |
| Patient had an important efficacy-related protocol violation | 4 | 7 | 4 | 8 | 23 |

(Source: Study Report 527.51 Final Report U09-3267-01; Table 11.1.1, page 78)

### 3.2.3 Efficacy Results

The sponsor's result for the primary efficacy endpoint for patients who were still on treatment (OT) at Week 14 is presented in Table 4. There was no statistically significant difference in the proportions of responders who achieved LPP < 40cm $H_2O$ between any tamsulosin HCl dose group and the placebo group at Week 14. The results from the analysis using the per-protocol population including non-completers as failures (NCF) were consistently similar to primary efficacy analysis using FAS-LPP population as presented in Table 5. We confirmed the sponsor's results using the same populations.

**Table 4: Response rates by treatment group at Week 14 (FAS-LPP, OT)**

| | | Tamsulosin Dose | | | |
|---|---|---|---|---|---|
| | Placebo | Low | Medium | High | Total |
| Number of Patients | 34 | 35 | 33 | 33 | 135 |
| LPP Responder N (%) | 12 (35.3) | 16 (45.7) | 9 (27.3) | 14 (42.4) | 51 (37.8) |
| Odds Ratio 95% CI | -- | 1.38 (0.50, 3.80) | 0.59 (0.20, 1.76) | 1.41 (0.50, 3.97) | -- |
| p-value | -- | 0.5388[1] | 0.3430[1] | 0.5209[1] | 0.9436[2] |

[1] Dose group vs. placebo

[2] Cochran-Armitage trend test

(Source: Study Report 527.51 Final Report U09-3267-01; Table 11.4.1.1:1, page 84)

**Table 5: Response rates by treatment group at Week 14 (FAS-LPP, NCF)**

| | | Tamsulosin Dose | | | |
|---|---|---|---|---|---|
| | Placebo | Low | Medium | High | Total |
| Number of Patients | 40 | 39 | 37 | 35 | 151 |
| LPP Responder N (%) | 12 (30.0) | 16 (41.0) | 9 (24.3) | 14 (40.0) | 51 (33.8) |
| Odds Ratio | -- | 1.42 (0.53, 3.78) | 0.63 (0.22, 1.83) | 1.62 (0.59, 4.43) | -- |
| p-value | -- | 0.4831[1] | 0.3972[1] | 0.3456[1] | 0.7141[2] |

[1] Dose group vs. placebo

[2] Cochran-Armitage trend test

(Source: Study Report 527.51 Final Report U09-3267-01; Table 11.4.1.1:3, page 85)

The results for secondary endpoints of change and percent change from baseline in LPP at Week 14 showed that there were no statistically significant difference between any dose group and the placebo group. We also confirmed that there were no statistically significant difference between any dose group and the placebo group for other listed secondary endpoints.

### 3.3 Evaluation of Safety

Details of safety analysis can be found in clinical reviewer's review.

# 4. FINDINGS IN SUBGROUP POPULATIONS

Subgroup analyses were performed for the primary efficacy endpoint by age category (2 to <5 years, 5 to <1 0 years and 10 to 16 years), weight (12.5 to <25.1 kg, 25.1 to <50.1 kg and 50.1 to 100 kg), geographic region groups and anti-cholinergic use on the FAS population. The results were consistent across these subgroups except the regions. The LLP response rate was significantly lower in Asian patients compared to patients in other regions as showed in Table 6, although the overall results were similar between treatment groups.

**Table 6: Response rates by region at Week 14 (FAS-LPP, OT)**

| | | | Tamsulosin vs. Placebo | | | |
|---|---|---|---|---|---|---|
| | | Placebo | Low | Medium | High | Total |
| All Region | LPP Responders/N (%) | 12/34 (35.3%) | 16/35 (45.7%) | 9/33 (27.3%) | 14/33 (42.4%) | 51/135 (37.8%) |
| | Odds Ratio (95% CI) | -- | 1.38 (0.50, 3.80) | 0.59 (0.20, 1.76) | 1.41 (0.50, 3.97) | |
| | p-value | -- | 0.54 | 0.34 | 0.52 | 0.94[1] |
| Asia | LPP Responders/N (%) | 4/20 (20.0%) | 6/18 (33.3%) | 4/17 (23.5%) | 7/20 (35.0%) | 21/75 (28.0%) |
| | Odds Ratio (95% CI) | -- | 2.01 (0.45, 8.96) | 1.20 (0.25, 5.82) | 2.28 (0.53, 9.68) | |
| | p-value | -- | 0.36 | 0.82 | 0.26 | 0.42[1] |
| Other Region | LPP Responders/N (%) | 8/14 (57.1%) | 10/17 (58.8%) | 5/16 (31.3%) | 7/13 (53.9%) | 30/60 (50.0%) |
| | Odds Ratio (95% CI) | -- | 1.07 (0.24, 4.70) | 0.34 (0.07, 1.55) | 0.68 (0.13, 3.41) | |
| | p-value | -- | 0.83 | 0.16 | 0.64 | 0.47[1] |

[1] Cochran-Armitage trend test

Source: Statistical Reviewer's Analysis

# 5. CONCLUSIONS

The results based on a single study shows that no statistically significant difference in efficacy, as measured by detrusor leak point pressure, between tamsulosin HCl and placebo treated patients, Efficacy outcome of this trial indicate that there is no therapeutic value of tamsulosin HCl as a treatment for pediatric patients with elevated detrusor leak point pressure associated with a known neurological deficit.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20579 | GI-1 | BOEHRINGER INGELHEIM PHARMACEUTICALS INC | FLOMAX (TAMSULOSIN HCL) 0.4MG CAPSULES |
| NDA-20579 | SUPPL-26 | BOEHRINGER INGELHEIM PHARMACEUTICALS INC | FLOMAX (TAMSULOSIN HCL) 0.4MG CAPSULES |

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