1 SYNOPSIS

Name of Sponsor/Company Ortho Urology, a unit of Ortho-McNeil Pharmaceutical, Inc. ***Name of Finished Product:*** Ditropan XL® ***Name of Active Ingredient:*** Oxybutynin chloride	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: A double-blind, randomized, parallel group trial of Ditropan XL® (oxybutynin chloride) extended release tablets or placebo in combination with Flomax® (tamsulosin hydrochloride) for the treatment of lower urinary tract symptoms

Investigators: Multiple

Study Centers: Multiple

Publication (reference): None

Study Period: ***Phase of Development: III***
Date of first enrollment: March 29, 2004
Date of last completed: June 22, 2005

Objectives: The objective of this study was to evaluate the safety and efficacy of Ditropan XL (oxybutynin chloride) in conjunction with an alpha-adrenergic blocker for the treatment of lower urinary tract symptoms.

Methodology: This was a placebo-controlled double-blind, randomized, multicenter, parallel group study. All subjects were treated with an alpha-adrenergic blocker, Flomax capsule 0.4 mg once daily, for at least four weeks prior to randomization. They were randomized to one of the following two treatment groups for 12 weeks of double-blinded treatment: Flomax 0.4 mg once daily plus Ditropan XL 10 mg once daily or Flomax 0.4 mg once daily plus placebo once daily.

A total of 420 male subjects were enrolled. Subjects were 45 years of age or older, with a clinical diagnosis of lower urinary tract symptoms (LUTS) with frequency and urgency with or without urge incontinence. Subjects were seen for their Screening Visit (Visit 1) up to four weeks prior to randomization to have a physical examination, medical history recorded, laboratory tests, International Prostate Symptom Score (I-PSS), and post-void residual (PVR) volume measured (with bladder scanner or ultrasound). If not previously treated with Flomax, subjects began treatment with Flomax at Visit 1. Subjects who met the eligibility criteria for this study returned for their Randomization Visit (Visit 2). At this visit, subjects had vital signs taken, adverse events recorded, the I-PSS reported as well as other questionnaires including the Symptom Problem Index (SPI), an Urgency and Frequency

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Scale, and an Incontinence Indicator. The PVR volume was measured (with bladder scanner or ultrasound) and a peak flow rate (PFR) was obtained. If a subject was on Flomax 0.4 mg/day for at least four weeks and a documented PVR volume within the past month was available, Visits 1 and 2 may have been combined but randomization did not occur until laboratory results were determined to be acceptable and all inclusion/exclusion criteria were met. Subjects returned for their follow-up visits after four weeks of treatment (Visit 3), after eight weeks of treatment (Visit 4), and at a Final Visit (Visit 5) after 12 weeks of treatment. At these follow-up visits, subjects had vital signs taken, adverse events recorded, the I-PSS reported as well as other questionnaires completed including the Participant-Reported Global Response Assessment (GRA) Scale, SPI, an Urgency and Frequency Scale, and an Incontinence Indicator. The PVR volume was measured (with bladder scanner or ultrasound) and a PFR was obtained. Physical examination was also performed at Visit 5. Subsequent to Protocol Amendment 1 (July 12, 2004), subjects were to be discontinued from the study if PFR decreased to <5 mL/sec or PVR volume reached >300 mL.

Safety was assessed by physical examinations performed at the screening and final visits. Adverse events, PFR, PVR volume, and vital signs were assessed throughout the study.

No interim analyses were performed.

Number of Subjects (planned and analyzed): The planned enrollment was approximately 350 men (175 subjects in the Ditropan XL group and 175 subjects in the placebo group). A total of 420 subjects were randomized to double-blind treatment; 409 were included in the efficacy analysis and 418 in the safety analysis.

Diagnosis and Main Criteria for Inclusion: Male subjects aged 45 years or older, with a clinical diagnosis of LUTS with frequency and urgency, with or without urge incontinence were eligible to participate. Main inclusion criteria included: after at least four weeks of 0.4 mg Flomax once daily, an I-PSS score ≥ 13 (Questions 1 through 7); an Irritative component (Questions 2, 4 and 7) score of the I-PSS ≥ 8; a PFR ≥ 8 mL/sec with a voided volume ≥ 125 mL; and a PVR volume ≤ 150 mL on two occasions.

Test Product, Dose and Mode of Administration, Batch Number: Study medication treatment was Ditropan XL 10 mg one oral tablet daily, Batch Numbers were: R12482 and R12713.

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Duration of Treatment: All subjects were treated with Flomax 0.4 mg/day oral capsule, for a minimum of four weeks before being randomized to either Flomax 0.4 mg once daily plus Ditropan XL 10 mg once daily or Flomax 0.4 mg once daily plus matching placebo. Subjects were instructed to take one capsule of Flomax and either one tablet of Ditropan XL or matching placebo orally every day for 12 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: Reference therapy consisted of one tablet daily of placebo, administered orally for 12 weeks. Placebo Batch Numbers were: R12483 and R12714.

Concomitant therapy consisted of Flomax 0.4 mg one capsule daily, administered orally for 12 weeks. Flomax Batch numbers were: L 0300139 and L 0400203.

Criteria for Evaluation:
Efficacy: Efficacy assessments were obtained at Screening (Visit 1), Baseline (Visit 2) and at Visits 3 through 5 of the Double-Blind Phase. All endpoints, primary and secondary, were calculated using observed values and the last observation carried forward (LOCF). The primary endpoint in this study was the change in total I-PSS score from baseline to Week 12 using the LOCF methodology.

The secondary endpoints included:

- Change in total I-PSS scores from baseline to Week 4 and Week 8
- Change in Irritability and Quality of Life I-PSS scores from baseline to Week 4, Week 8, and Week 12
- Change in total SPI score from baseline to Week 4, Week 8, and Week 12
- Change in Urgency and Frequency Scale scores from baseline to Week 4, Week 8, and Week 12
- Change in Incontinence Indicator score from baseline to Week 4, Week 8, and Week 12
- GRA Scale score at Week 4, Week 8, and Week 12
- Percent responders (25% decrease from baseline in I-PSS total score) at Week 4, Week 8, and Week 12

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Safety: The safety assessments evaluated were PFR, PVR volume, adverse events, vital signs and physical examinations.

Statistical Methods: All statistical tests were performed at the two-sided, 5% significance level.

For the primary endpoint, an analysis of covariance (ANCOVA) model was applied for treatment comparison with visit score as the dependent variable, baseline total I-PSS score as a covariate, and treatment and center as qualitative design factors.

All secondary endpoints (except GRA and responders) were descriptively summarized (count, mean, median, standard deviation, minimum and maximum) at baseline and for each visit. The change from baseline at each visit was also summarized. All secondary endpoints, except GRA and the percent of responders, were analyzed using ANCOVA with visit score as the dependent variable, baseline score as a covariate, and treatment and center as qualitative design factors. The least squares means at each visit for each treatment group were also presented. In addition to the ANCOVA, the Incontinence Indicator was analyzed using a Cochran-Mantel-Haenszel test with modified ridit scores and stratifying on center. The average of the change scores for each secondary endpoint was presented in a line graph across the three post-baseline visits by treatment group.

Responders were summarized at each visit with counts and percents. The percent of responders at each visit was analyzed using Fisher's Exact test. Subject responses to the GRA Scale were summarized at each visit with counts and percents. Responses to the GRA Scale were analyzed using a Cochran-Mantel-Haenszel test with modified ridit scores and stratifying on center. The percent of responses at each visit was summarized on bar graphs for each treatment group.

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Efficacy Results:

The mean age of the ITT population was 62.8 years and 90.5% of subjects were white. The mean time since LUTS diagnosis was 5.0 years. Overall, 49.6% of subjects had a baseline I-PSS score of moderate and 50.4% were severe. In addition, 96.3% of subjects had a baseline PFR ≥8 mL/sec and 99.3% had a baseline PVR volume of ≤150 mL. No statistically significant differences between the treatment groups were observed for any of the demographic or baseline characteristics including baseline LUTS and functional measures.

Table 1-1 presents a summary of primary and secondary efficacy results (LOCF) for subjects in the ITT population. Male subjects with LUTS receiving Ditropan XL 10 mg/day in conjunction with Flomax 0.4 mg/day had a statistically significantly greater improvement in least squares adjusted mean total I-PSS score from baseline to Week 12 (primary endpoint) compared with subjects receiving placebo plus Flomax, 13.41 and 15.10, respectively, p=0.006. Although not statistically significant, the treatment groups began to separate at Week 4 and continued to diverge over time; the difference between treatment groups reached statistical significance at Week 8 (least squares adjusted mean I-PSS LOCF total score: 14.52 for Ditropan XL and 15.79 for placebo, p=0.033) and also at Week 12 (the primary endpoint). Similar results were noted for the analysis of observed results. Efficacy results were consistent over time across all endpoints.

Ditropan XL was statistically significantly superior to placebo at Weeks 4, 8, and 12 for those secondary endpoints that evaluated LUTS including change from baseline in: Irritability and Quality of Life I-PSS scores, Urgency and Frequency Scale scores, and Incontinence Indicator score. Ditropan XL was statistically significantly superior to placebo for the change in total SPI score from baseline to Week 8 and Week 12.

At Weeks 8 and 12, statistically significant differences were noted in GRA Scale score in subjects treated with Ditropan XL compared with placebo. A greater proportion of subjects treated with Ditropan XL assessed their condition as slightly better, moderately better or markedly better (74.9% at Week 8 and 75.9% at Week 12) compared to subjects treated with placebo (62.6% at Week 8 and 63.1% at Week 12). A statistically significantly greater proportion of subjects treated with Ditropan XL were responders (61.6%) compared to subjects treated with placebo (51.0%) at Week 12.

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Table 1-1. Summary of Efficacy Results From the Last Observation Carried Forward Analysis for Subjects in the Intent-to-Treat Population

	Week 4		Week 8		Week 12	
Measure	Ditropan XL	Placebo	Ditropan XL	Placebo	Ditropan XL	Placebo
I-PSS Total Score[a], mean	15.91	16.54	14.52	15.79	**13.41**	**15.10**
p-Value		0.237		0.033		**0.006**
I-PSS Irritability Score, mean	7.58	8.26	6.89	7.95	6.43	7.66
p-Value		0.008		<0.001		<0.001
I-PSS Quality of Life Score, mean	3.21	3.55	2.93	3.42	2.82	3.27
p-Value		0.006		<0.001		0.001
Symptom Problem Index Total Score, mean	12.32	13.16	11.29	12.54	10.49	11.65
p-Value		0.093		0.017		0.037
Urgency Score, mean	4.68	5.35	4.00	5.08	3.71	4.58
p-Value		0.004		<0.001		<0.001
Frequency Score, mean	4.81	5.39	4.20	5.12	4.16	4.84
p-Value		0.009		<0.001		0.007
Incontinence Indicator Score, mean	1.96	3.00	1.79	2.69	1.69	2.60
p-Value		<0.001		<0.001		<0.001
Global Response Assessment[b], %	71.4%	68.9%	74.9%	62.6%	75.9%	63.1%
p-Value		0.109		<0.001		0.016
Responders[c], %	44.9%	36.9%	53.2%	46.6%	61.6%	51.0%
p-Value		0.106		0.199		0.036

a: The mean I-PSS score at Week 12 was the primary efficacy variable (results in bold).
b: Percentage of subjects who assessed their condition as slightly better, moderately better or markedly better.
c: Percentage of subjects who had a ≥25% reduction from baseline in I-PSS total score.

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Safety Results:

All study medications were well tolerated. Adverse events were reported by 89 (42.6%) subjects in each of the two treatment groups, Ditropan XL 10 mg/day plus Flomax 0.4 mg/day and placebo plus Flomax 0.4 mg/day groups, p=1.000. Dry mouth was the most common adverse event reported and was the only adverse event reported statistically significantly more frequently in the Ditropan XL group (15.3%) than in the placebo group (4.8%), p<0.001. This event was consistent with the known anticholinergic effects of Ditropan XL. Five subjects (2.4%) in the Ditropan XL group and six subjects (2.9%) in the placebo group reported serious adverse events. None were considered to be drug-related. Twenty-one (10.0%) subjects in the Ditropan XL group and 20 (9.6%) subjects in the placebo group withdrew from the study due to adverse events that occurred during the randomized phase. In addition, two subjects in the placebo group withdrew from the study during the randomized phase due to an adverse event that was reported prior to randomization. One subject treated with Ditropan XL died during the study. The investigator considered the death due to sepsis, aspiration pneumonia, and atrial fibrillation to be unrelated to study drug. No statistically significant differences between treatment groups were observed for change from baseline in mean PFR at Weeks 4, 8, and 12. While not statistically significant (p=0.493), the incidence of reduced PFR (<5 mL/sec) was 3.8% (n=8) in subjects receiving Ditropan XL plus Flomax and 5.7% (n=12) in subjects receiving placebo plus Flomax. Mean PVR volumes were statistically significantly greater in the Ditropan XL group compared with the placebo group at Week 4, 67.26 mL and 49.80 mL, respectively (p=0.002), and at Week 12, 69.10 mL and 54.88 mL, respectively (p=0.023). The overall increase in mean PVR volume was mild and consistent with known anticholinergic effects of DITROPAN XL. While not statistically significant (p=0.122), the incidence of urinary retention (post-baseline PVR >300 mL) was higher in subjects receiving Ditropan XL plus Flomax (n=6, 2.9%) than in subjects receiving placebo plus Flomax (n=1, 0.5%).

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Conclusions:

- Male subjects with LUTS receiving Ditropan XL 10 mg/day in conjunction with Flomax 0.4 mg/day had a statistically significantly greater improvement in total I-PSS score from baseline to Week 12 (primary endpoint) compared with subjects receiving placebo plus Flomax.

- Ditropan XL 10 mg/day, when administered in conjunction with Flomax 0.4 mg/day, was statistically significantly superior to placebo plus Flomax for those secondary endpoints that evaluated LUTS including:
    - Change in total I-PSS score from baseline to Week 8
    - Change in Irritability and Quality of Life I-PSS scores from baseline to Week 4, Week 8, and Week 12
    - Change in total SPI score from baseline to Week 8 and Week 12
    - Change in Urgency and Frequency Scale scores from baseline to Week 4, Week 8, and Week 12
    - Change in Incontinence Indicator score from baseline to Week 4, Week 8, and Week 12
    - GRA Scale score at Week 8 and Week 12
    - Proportion of responders at Week 12

- Efficacy results were consistent over time and across all endpoints.

- Ditropan XL 10 mg/day plus Flomax 0.4 mg/day and placebo plus Flomax were well tolerated. One subject in the Ditropan XL group died during the study; the death was considered by the investigator to be unrelated to study drug. Five subjects in the Ditropan XL group and six subjects in the placebo group reported serious adverse events; none were considered to be drug-related.

- Dry mouth was the most common adverse event reported and was the only adverse event reported statistically significantly more frequently in the Ditropan XL group than in the placebo group, $p<0.001$. This event was consistent with the known anticholinergic effects of Ditropan XL.

Date of the Report: January 5, 2006

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