CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-351

MEDICAL REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Original NDA

NDA	21-351
Sponsor	Watson Laboratories, Inc.-Utah 417 Wakara Way Salt Lake City, Utah 84108
Submission Type	Original NDA
Drug	
Established name	Oxybutynin transdermal system (TDS)
Trade name	Oxytrol™
Chemical name	4-(diethylamino)-2-butyn-1-yl-phenylcyclohexylglycolate
Drug Class	Anticholinergic (3011050)
Proposed Indication	Treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Route of Administration	Transdermal
Dosage Form	Transdermal system (TDS)
Dosing Regimen	One TDS applied to abdominal skin twice weekly (every 3 to 4 days)
Dose	[redacted] 39 cm^2 transdermal system
Dates	
Submitted	April 26, 2001
CDER stamp date	April 26, 2001
PDUFA date	March 26, 2002 (11 month)
Related NDAs	NDA 17-577 (Ditropan®-oxybutynin chloride 5 mg tablets) NDA 18-211 (Ditropan®-oxybutynin chloride syrup 5 mg/5mL) NDA 20-771 (Detrol®-tolterodine 1 and 2 mg tablets) NDA 20-897 (Ditropan® XL, oxybutynin chloride extended release 5, 10, 15 mg tablets) NDA 21-228 (Detrol® LA-tolterodine 2 and 4 mg extended release capsules)
Related INDs	[redacted] IND 50,489 (oxybutynin transdermal system; Theratech)
Medical Reviewer	Brenda Gierhart, MD
Date Review Completed	March 26, 2002

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EXECUTIVE SUMMARY

1 RECOMMENDATIONS

1.1 Recommendation Regarding Approval

1.1.1 Approvability

It is recommended that the oxybutynin transdermal system (NDA 21-351) receive a not approvable action, based on inadequate efficacy demonstrated in the Primary Clinical Studies **O99009** (Phase 3) and **O96017** (Phase 2). It is the reviewer's opinion that the sponsor submitted quite limited evidence of efficacy in one trial, Study **O99009**, for one dose, oxybutynin 39 cm^2 transdermal system (TDS). The primary endpoint for Study **O99009** (number of urinary incontinence episodes) demonstrated statistical significance only for oxybutynin 39 cm^2 TDS after adjusting the p-value for multiple comparisons with the Dunnett's test. A directed Division of Scientific Investigations (DSI) inspection at Site #12 (Dr. Brian Feagins) for Study **O99009** revealed serious regulatory violations, a Form 483 was issued, and DSI recommended that Study **O99009** data from Dr. Feagin's site not be used in support of this NDA. After adjusting the p-value for multiple comparisons with the Dunnett's test and deleting Site #12 from the analysis of Study **O99009**, the key secondary endpoint for Study **O99009** (urinary frequency) did not demonstrate statistical significance for any dose of oxybutynin TDS.

DSI inspection at Site #03 (Dr. Joseph Antoci) for Study **O99009** uncovered data transcription discrepancies, which resulted in the sponsor confirming that efficacy data at multiple sites from at least 25 and possibly 35 urinary diaries had missing pages or used the incorrect baseline urinary diaries. DSI also issued a Form 483 to Study **O99009** Site #21 (Dr. Ira Klimberg) after the inspector noted that certain efficacy data for Subjects #2105 and 2122 had not been obtained, however the investigator falsely stated that it had been obtained. In addition, the sponsor changed the primary analysis in the Statistical Analysis Plan (SAP) from the DRUDP requested intent to treat (ITT) population to a modified intent to treat (mITT population), where each patient was grouped by the treatment actually received.

In the future, if the sponsor opts to resubmit Study **O99009**, the reviewer recommends that the data be reanalyzed by the sponsor for the ITT population, excluding data from Site #12, excluding data for Subjects #2105 and 2122, and utilizing the correctly transcribed urinary diaries and the correct baseline urinary diaries efficacy data.

1.1.2 Basis for Recommendation Regarding Approvability (Risk/Benefit Analysis)

The sponsor has not provided "substantial evidence" to establish the effectiveness of the oxybutynin transdermal system, as required by Section 505(d) of the Federal Food, Drug, and Cosmetic Act. The sponsor conducted a single adequate and well-controlled efficacy study to support approval, Study O99009. The characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim include a statistically very persuasive finding.[1] Data from the Phase 3 Study O99009 did not demonstrate statistical significance for the critical secondary endpoint of urinary frequency after Site #12 was deleted at the recommendation of DSI.

In addition, Study O99009 was not supported by additional evidence. Transdermal oxybutynin was not confirmed as being equivalent to oral oxybutynin by blood levels. The efficacy of transdermal oxybutynin was not found to be equivalent to oral oxybutynin in the Phase 2 Study O96017.

In Study O99009 over the 12-week double-blind treatment period for the primary efficacy endpoint of urinary incontinence episodes:

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998, pg 15.

- mean and median change-from-baseline of overactive bladder patients in the oxybutynin low and medium-dose TDS groups (13 cm^2 and 26 cm^2) were not statistically improved compared with the placebo group; the mean and median change-from-baseline in the oxybutynin medium-dose (26 cm^2) TDS group were actually worse than placebo
- mean change-from-baseline in the oxybutynin high-dose (39 cm^2) TDS group was not statistically improved compared with the placebo group
- median change-from-baseline in the oxybutynin high-dose (39 cm^2) TDS group demonstrated a statistically significant improvement over placebo when the p-value was adjusted for multiple comparisons by the Dunnett's test and data from all sites were used, as well as when the data from Site #12 was deleted. However, the demonstrated difference from placebo for the oxybutynin 39 cm^2 was only 4.5 episodes of urinary incontinence per week, or 0.64 episodes per day
- median improvement of 4.5 urinary incontinence episodes per week is significantly less than the improvement shown with other currently approved overactive bladder medical therapeutic options in other trials from other NDAs; this reviewer acknowledges the inherent weaknesses of such comparisons, nevertheless, the reviewer considers this improvement to not be clinically significant.

In Study **O99009** over the 12-week double-blind treatment period for the key **secondary efficacy endpoint** of urinary frequency:

- mean and median change-from-baseline in the oxybutynin 13 and 26 cm^2 TDS groups were not statistically improved compared with the placebo group
- mean change-from-baseline in the oxybutynin 39 cm^2 TDS groups was not statistically improved compared with the placebo group
- median change-from-baseline in the oxybutynin 39 cm^2 TDS groups was not statistically improved compared with the placebo group when the p-value was adjusted for multiple comparisons by the Dunnett's test and patients from Site #12 were removed from the analysis.

A directed DSI inspection at Site #12 (Dr. Brian Feagins) for Study **O99009** revealed serious regulatory violations, a Form 483 was issued, and DSI recommended that Protocol O99009 data from Dr. Feagin's site not be used in support of this NDA.

DSI inspections for Study **O99009** also found that at Site #03 (Dr. Joseph Antoci) there were data transcription discrepancies, which resulted in the sponsor confirming that efficacy data from at least 25 and possibly 35 urinary diaries had been incorrectly transcribed at multiple sites. DSI also issued a Form 483 to Study **O99009** Site #21 (Dr. Ira Klimberg) after the inspector noted that certain efficacy data had not been obtained, however the investigator falsely stated that it had been obtained. Nevertheless, DSI concluded that the data submitted in support of this NDA by Dr. Klimberg appeared acceptable.

It should be noted that the prespecified Statistical Analysis Plan (SAP) for Study **O99009** was for a parametric ANCOVA analysis (i.e. means), however the sponsor also evaluated the data by non-parametric ranking procedure (i.e. medians) after it was noted that the distributional normality assumption failed to hold for the diary data. While this analysis was not the pre-defined analysis, our Division of Biometrics believed the change was reasonable based on the distribution of the data.

After it was noted that 6 patients were correctly randomized yet received the incorrect treatment, the sponsor changed the primary analysis in the Statistical Analysis Plan (SAP) from the intent to treat (ITT) population to a modified intent to treat (mITT population), where each patient was grouped by the treatment actually received. This change in the SAP, which occurred after the last patient

completed the double-blind period (Part 1) of Study O99009, is concerning to the reviewer. The sponsor had been directed by DRUDP at the pre-NDA meeting to base the primary efficacy analysis on the intent to treat (ITT) population. Finally, Study **O99009** appeared to be underpowered.

The Phase 2 Study **O96017** failed on the primary efficacy endpoint, equivalence in the responder rate for the oral and transdermal oxybutynin groups, in both the evaluable and intent-to-treat analysis populations. Finally, Study **O96017** was underpowered.

Therefore, at best, the sponsor has shown limited evidence of efficacy for only one key endpoint in one trial for one dose, oxybutynin 39 cm^2 TDS, and this evidence did not reach statistical significance when the data from Site #12 was deleted. There is no confirmatory evidence for this finding.

The **Safety Profile** of the oxybutynin transdermal system is probably adequate for approval, however skin tolerability issues are a concern, a limited safety database was submitted, and no controlled assessment of cumulative irritation potential using the 39 cm^2 system was submitted. Application site adverse events were reported by 120 (22%) of the 542 patients receiving transdermal oxybutynin in the integrated safety studies and 43 of these patients withdrew due to application site adverse events. If safety data from when the patients were treated with the ineffective oxybutynin 13 and 26 cm^2 TDS doses were deleted, the remaining safety database for the oxybutynin 39 and 52 cm^2 TDS groups is quite limited. The extensive data previously submitted for oral oxybutynin must be taken into consideration.

The safety database does demonstrate less dry mouth associated with transdermal oxybutynin than reported previously with oral oxybutynin, however it remains unclear what dose of transdermal oxybutynin is equivalent in efficacy to any particular dose of oral oxybutynin. The reviewer believes that some of the decreased incidence of dry mouth is due to the use of ineffective doses of transdermal oxybutynin.

1.2 Specific Recommendations to the Sponsor

- Prior to approval of oxybutynin transdermal for use in the overactive bladder population, the sponsor will need to provide additional evidence of efficacy from at least one new Phase 3 trial.
- Sponsor to consider increasing the dose beyond the proposed oxybutynin 39 cm^2 TDS to increase the efficacy.
- Sponsor is advised to explore options for decreasing the TDS size.
- In any future resubmission of Study **O99009**, the data should be reanalyzed for the ITT population, excluding data from Site #12, excluding data for Subjects #2105 and #2122, and utilizing the correctly transcribed urinary diaries and the correct baseline urinary diaries efficacy data.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

2.1.1 Drug

Oral oxybutynin is approved for the treatment of overactive bladder symptoms, however its use has been limited by its associated anticholinergic side effects, such as dry mouth and constipation. Transdermal oxybutynin was developed to reduce the symptoms of overactive bladder while minimizing side effects. The potential for transdermal oxybutynin to improve the anticholinergic side effect profile is presumed to result from avoiding presystemic metabolism in hepatic and intestinal enzyme systems. Bypassing the presystemic metabolism results in lower levels of the primary oxybutynin metabolite, N-desethyloxybutynin, which may cause the anticholinergic side effects. However, N-desethyloxybutynin is also an active metabolite and may be responsible for much of the

pharmacological activity of the drug.[2] The sponsor states that the transdermal system offers an advantage over current oral formulations with regard to patient compliance due to less frequent administration and less variability in the drug and metabolite plasma concentrations.

Oxybutynin is a chiral molecule that exists in two enantiomeric forms (R and S). In-vivo and animal studies have been conducted with conflicting results regarding whether the pharmacological effects and anticholinergic activities of racemic oxybutynin are attributable primarily to the R or S isomer.[3,4]

2.1.2 Clinical Program

Data from one Phase 3 (O99009) and one Phase 2 (O96017) clinical studies were submitted by the sponsor to primarily support the efficacy and safety of transdermal oxybutynin. Both studies were conducted in women and men with overactive bladder.

2.1.3 Design of the Controlled Studies

Study O99009 was designated by the sponsor as the principal efficacy and safety study, with **Study O96017** as a supporting study.

Study O99009 was a multicenter clinical trial that consisted of three treatment periods. An initial 12-week active treatment, placebo controlled, randomized, double blind period (Part I) was followed by a 12-week open-label, dose-titration safety period (Part II), and then followed by a 28-week open-label safety extension (Part III). A total of 520 patients with urge urinary incontinence (U-UI) at 40 US sites were randomly assigned in a 1:1:1:1 ratio to treatment with either oxybutynin 13, 26, or 39 cm^2 TDS or placebo TDS. The primary efficacy endpoint was the change from baseline to endpoint during the 12-week double blind period (Part I) in the number of urinary incontinence episodes per week recorded in the 7-day urinary diary by patients receiving active treatment versus those receiving placebo. Patients underwent efficacy and safety assessments at monthly or more frequent intervals.

Study O96017 was a 6-week active treatment, active controlled, randomized, double blind, dose-titration, multicenter clinical trial intended to demonstrate equivalence in responder rates between transdermal and oral oxybutynin. A total of 76 patients with urge incontinence associated with detrusor instability or detrusor hyperreflexia who had demonstrated symptomatic improvement on prior treatment with oral oxybutynin were enrolled in the study. The primary efficacy endpoint was the percentage of patients categorized as responders to treatment in each study group after a minimum of 4 weeks of treatment was established. Patients were categorized as responders or non-responders to treatment based on the difference in the number of incontinence episodes reported prior to and during treatment. Responders demonstrated a >30% decrease from baseline to endpoint in the number of daily incontinence episodes as recorded on their individual 3-day urinary diary.

Medical Officer's Comment

The reviewer believes this study would have benefited from a placebo arm to confirm whether or not placebo subjects demonstrated similar responder rates to treated groups.

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[2] Yarker Y et al. Oxybutynin A Review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging*. 1995; 6 (3): 245.

[3] Noronha-Blob L and Kacher J. Enantiomers of Oxybutynin: *In Vitro* Pharmacological Characterization at M_1, M_2 and M_3 Muscarinic Receptors and *in Vivo* Effects on Urinary Bladder Contraction, Mydriasis and Salivary Secretion in Guinea Pigs. *J Pharmacology and Experimental Therapeutics*. 1991; 256 (2): 582-567.

[4] Kachur J et al. R and S Enantiomers of Oxybutynin: Pharmacological Effects in Guinea Pig Bladder and Intestine. *J. Pharmacology and Experimental Therapeutics*. 1988; 247 (3): 867-872.

2.2 Efficacy

2.2.1 Efficacy Assessments and Efficacy Endpoints

In each of the two primary oxybutynin clinical trials, there was one primary efficacy endpoint based on urinary diary data and several secondary endpoints, based primarily on urinary diary data, global disease state assessment, or Quality of Life (QoL) assessments.

2.2.2 Efficacy Results (Primary Endpoint)

The one primary efficacy endpoint in the principal efficacy trial **O99009** was:

> **Change from baseline to endpoint in the 12-week double blind period in the number of urinary incontinence episodes per week recorded in the 7-day urinary diary by patients receiving active treatment versus those receiving placebo**

At the baseline, the **median** number of urinary incontinence per week was 30 to 31 among the four groups. During the 12-week double blind period (Part I), placebo treated patients showed an improvement of 14.5 episodes less per week. In contrast, 15.0, 14.0, and 19.0 episodes less per week were observed in the oxybutynin 13, 26, and 39 cm^2 TDS groups, respectively. The oxybutynin 13 and 26 cm^2 groups failed to differentiate from placebo. The oxybutynin 26 cm^2 TDS group demonstrated less improvement than the placebo group. The oxybutynin 39 cm^2 TDS group demonstrated a statistical significance in change from baseline to end of treatment in the **median** ($p=0.0165$) but not in the **mean** ($p=0.2831$) difference from placebo, after adjusting the p-values for multiple comparison's with the Dunnett's test. The pre-defined statistical analysis plan called for a comparison of means. The sponsor undertook a post-hoc comparison of medians based upon the distribution of the data. Our Division of Biometrics agreed that such a change in the SAP was reasonable.

Medical Officer's Comment

The reviewer does not believe that the median decrease of 4.5 episodes of urinary incontinence per week, as demonstrated in the oxybutynin 39 cm^2 TDS group, is a clinically significant difference from placebo.

The one primary efficacy endpoint in the supporting efficacy trial **O96017** was:

> **Percentage of patients categorized as responders to treatment in each study group after a minimum of 4 weeks of treatment**

Patients were categorized as responders or non-responders to treatment based on the difference in the number of incontinence episodes reported at Week 6 compared to the pretreatment period. Patients were included in the primary analysis population (i.e. evaluable patients) if they completed at least four weeks of treatment. Responders demonstrated a >30% decrease from baseline to endpoint in the number of daily incontinence episodes as recorded on their individual 3-day urinary diary. It is important to note that 68% of all patients in the TDS group up-titrated to the 52 cm^2 patch, a dose not being considered for approval. The sponsor reported that 86% of transdermal treatment patients responded to treatment versus 89% of the oral group, yielding a 95% confidence interval for the mean difference of -17.3% to +13.2 %, which fell outside the prespecified equivalence margin of 15%. When performing the prespecified statistical analysis, Study **O96017** failed on its primary efficacy endpoint, equivalence in the responder rate for the oral and transdermal oxybutynin groups, in both the evaluable and intent-to-treat analysis populations and this despite most patients using a 52 cm^2 patch.

2.2.3 Other Efficacy Issues

After adjusting the p-value for multiple comparisons with the Dunnett's test and deleting Site #12 from the analysis, no statistically significant mean or median difference from placebo was shown in

any oxybutynin TDS group for the Study **O99009** key secondary efficacy outcome "average daily urinary" in the double blind period (Part I). A statistically significant mean and median change in average urinary volume per void was seen in the oxybutynin 26 and 39 cm^2 TDS groups when compared to placebo during the double blind period (Part 1). The **median** change from baseline for the placebo group was 6 mL, for the oxybutynin 26 cm^2 TDS group was 19 mL and for the 39 cm^2 TDS group was 24 mL. If Site #12 was omitted from the mITT cohort, the statistical significance for volume voided for the oxybutynin 26 and 39 cm^2 treatment groups was maintained. Volume voided appeared to increase in both the 26 cm^2 and 39 cm^2 groups compared to placebo. In the management of patients with overactive bladder, this reviewer believes that such increases do not reflect meaningful clinical benefit. No statistically significant findings resulted from the global assessment of disease state analysis in Study **O99009**.

2.2.4 Proposed Label Claim

Review of the sponsor's proposed labeling will be completed after oxybutynin TDS is found to be approvable.

2.3 Safety

2.3.1 *Exposure to Study Drug*

At the time of NDA submission, a total of 855 subjects (542 patients and 313 healthy volunteers) had received at least one dose of oxybutynin TDS. In the integrated safety studies, a total of 542 overactive bladder patients and 83 healthy volunteers were exposed to any dose of oxybutynin TDS, of which:

- 436 overactive bladder patients were exposed to oxybutynin 26 cm^2 TDS
- 24 healthy volunteers were exposed to oxybutynin 26 cm^2 TDS
- 331 overactive bladder patients were exposed to oxybutynin 39 cm^2 TDS
- 68 healthy volunteers were exposed to oxybutynin 39 cm^2 TDS

It should be noted that any one patient could have been, and probably was, included in the exposure totals for more than one dose of oxybutynin TDS.

Prolonged exposure to oxybutynin TDS only occurred during Protocol **O99009** and it was as follows[5]:

- 46 patients were exposed for at least 26 weeks (i.e. 6 months) to oxybutynin 26 cm^2 TDS
- 0 patients were exposed for at least 52 weeks (i.e. at least 1 year)) to oxybutynin 26 cm^2 TDS
- 64 patients were exposed for at least 26 weeks (i.e. 6 months) to oxybutynin 39 cm^2 TDS
- 1 patient was exposed for at least 52 weeks (i.e. 1 year) to oxybutynin 39 cm^2 TDS

Patients were monitored monthly or more frequently throughout the treatment period. Overall, this is a small safety database.

Medical Officer's Comment

The extensive data previously submitted for oral oxybutynin and a comparison of systemic exposures between TDS and oral formulations must be taken into consideration.

[5] 120-Safety Update Report Table 14.3.5.1.4.3 in Vol. 1 on pg. 461-462

2.3.2 General Safety Findings

The types of the reported adverse events and the proportion of patients reporting them in the clinical trials were generally as expected in healthy volunteers or overactive bladder subjects being treated with oxybutynin TDS.

The overall incidence of treatment-emergent AEs in the integrated safety studies was somewhat greater in overactive bladder patients on the active TDS (73.1%) compared to the placebo TDS (62.1%). Drug-related AEs were also more common in patients on the active TDS (46.3%) than TDS placebo-treated patients (32.6%), with a trend toward higher incidence of AEs with increasing dose (21.9% with 13 cm^2, 23.4% with 26 cm^2, and 28.1% with 39 cm^2). The most common drug-related adverse events were application site reactions (22.7% of active TDS patients; 9.1% of placebo TDS patients) and dry mouth (9.4% of active TDS patients; 8.3% of placebo TDS patients) in the integrated safety studies.

Medical Officer's Comment

The comparability of incidences for "dry mouth" between drug and placebo is notable and could ultimately reflect a real benefit of this type of treatment.

Overall, 81 (14.9%) of 542 active TDS patients in the integrated safety studies discontinued treatment due to adverse events and 67 (12.4%) of these 542 patients discontinued due to treatment-related AEs. Discontinuation rates tended to increase with increasing duration of exposure.

The primary reason for discontinuations due to AEs in the active TDS integrated safety studies group was application site adverse events (43 of 542 patients or 7.9%). In the integrated studied active TDS patients, discontinuation due to application site AEs increased with dose from 2.7% in the 13 cm^2 group to 4.8% in the 39 cm^2 group. In the TDS placebo group, only 1 patient discontinued due to an application site AE.

During the double blind period of Study O99009 (Part I), a total of 41 of 520 (7.9%) patients were withdrawn because of a treatment-related adverse event with the treatment groups as follows:

- 2 of 132 (1.5%) patients in the placebo group
- 13 of 130 (10%) patients in the oxybutynin 13 cm^2 TDS group
- 12 of 133 (9%) patients in the oxybutynin 26 cm^2 TDS group
- 14 of 125 (11.2 %) patients in the oxybutynin 39 cm^2 TDS group

Changes in safety laboratory values also were generally similar across the treatment groups.

2.3.3 Patient Deaths or Pregnancy

No patients died in the uncontrolled studies. Two patients died in the controlled studies, however one death occurred before treatment began and the other occurred following study participation. Neither death was attributed to treatment with oxybutynin TDS. One patient became pregnant during O99009 and miscarried. She had been treated with oxybutynin 26 cm^2 TDS, however her miscarriage was felt to be unrelated to her treatment.

2.3.4 Safety Issues of Particular Concern

During clinical trials with transdermal oxybutynin, three safety concerns were identified: skin tolerability, electrocardiograms, and post-void residual urine volume. Only skin tolerability was felt to be a significant safety concern.

2.4 Dosing

The efficacy of oxybutynin transdermal may increase to adequate levels if the dose is increased beyond what is delivered by the oxybutynin 39 cm^2 TDS. However, patient intolerance of the resultant larger TDS size and the known skin tolerability issues may prevent this increase in dose.

2.5 Special Populations

Transdermal oxybutynin is to be used for adult patients with overactive bladder. The target population will primarily be older women. The sponsor did not enroll sufficient men or minorities to perform an adequate subset safety analysis based on sex or race from the controlled safety studies data. An adequate subset safety analyses for age <65 and ≥65 years was performed and no obvious differences were identified. Studies were not conducted in pediatric subjects or in subjects with renal impairment, liver insufficiency, or other disease states.

CLINICAL REVIEW

3 INTRODUCTION AND BACKGROUND

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3.1 Drug

- **Established Name** Oxybutynin transdermal system
- **Proposed Trade Name** Oxytrol™
- **Chemical Name** 4-(diethylamino)-2-butyn-1-yl-phenylcyclohexylglycolate
- **Drug Class** Anticholinergic
- **Proposed Indication** Oxytrol™ is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.
- **Dose** Oxybutynin —— transdermal system

  Oxybutynin 39 cm^2 transdermal system
- **Dosing Regimen** One transdermal system applied to abdominal skin twice weekly (every 3 to 4 days)

3.2 Overview of Disease and Treatment Options

3.2.1 Overactive Bladder

Drs. Abrams and Wein have offered the following definition of overactive bladder:

> The overactive bladder is a medical condition referring to the symptoms of frequency and urgency, with or without urge incontinence, when appearing in the absence of local pathologic or metabolic factors that would account for these symptoms. Incontinence is not a necessary condition for diagnosis because roughly half of the people with overactive bladder do not have incontinence.[6]

The number of people suffering from overactive bladder has been estimated to be between 50 and 100 million worldwide.[1] A recent Gallup study showed that the incidence consistently increases with advancing age.[1] Treatment options include behavioral modification techniques, such as timed voiding, bladder drills, and prompted voiding, pelvic-floor exercises, pharmacological therapy, and

[6] Abrams P and Wein A. Introduction: Overactive Bladder and Its Treatments. *Urology*. 2000; 55 (5A): 1-2.

surgery.[7,8] Anticholinergic therapy with immediate-release oxybutynin chloride (Ditropan®) has been the mainstay of medical treatment for overactive bladder for almost 30 years.[9] . Oxybutynin is a racemic mixture of two optical isomers, designated R and S. Although the efficacy of oxybutynin is well documented, the anticholinergic side effects of dry mouth, constipation, accommodation disturbances, and blurred vision often lead to poor compliance or withdrawal from therapy.[10] A controlled-release oxybutynin (Ditropan® XL) was developed in hopes of improving patient compliance. Tolterodine tartrate immediate release tablets (Detrol®) and extended release capsules (Detrol® LA) were also developed for their potential improvement in patient compliance. The efficacy and safety of tolterodine for overactive bladder has been demonstrated in multiple clinical trials[11,12], however the approved product labeling for Detrol® and Detrol® LA do not include any comparative statements to oxybutynin.

3.2.2 Medical Treatment of Overactive Bladder

NDA 17-577 for **Ditropan®** (oxybutynin chloride) 5 mg **tablets** was approved on July 16, 1975.

NDA 18-211 for **Ditropan®** (oxybutynin chloride) 5 mg/5 mL **syrup** was approved on November 29, 1979.

NDA 20-897 for **Ditropan® XL** (oxybutynin chloride extended release) 5, 10, and 15 mg extended release **tablets** was approved on December 16, 1998.

NDA 20-771 for **Detrol®** (tolterodine tartrate) 1 and 2 mg **tablets** was approved on March 25, 1998.

NDA 21-228 for **Detrol® LA** (tolterodine tartrate extended release) 2 and 4 mg **capsules** was approved on December 22, 2000.

3.3 Important Milestones in the Development of Oxybutynin Transdermal System

3.3.1 Significant Regulatory Interactions and Decisions

IND 50,489 for — (oxybutynin transdermal system: matrix-type formulation) was filed by Theratech, Inc. on May 2, 1996. The — oxybutynin transdermal systems were designed for the continuous administration of oxybutynin over a 3-4 day period. Each original system consisted of three layers. Layer 1 (top layer) was a thin polyester/ethylene-vinyl acetate (PET/EVA) film. Layer 2 (next to the skin) was a cast film of — acrylic adhesive that was formulated to contain the oxybutynin free base (13.1 mg in 10 cm^2) and triacetin, USP as a non-active excipient. Triacetin was added to — Layer 3 was two overlapped polyester (PET) release liner strips designed to be peeled off and discarded prior to applying the matrix system. TheraTech proposed that transdermal delivery would offer several advantages over oral oxybutynin administration as follows:

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[7] Davila G et al. A Short-term, Multicenter, Randomized, Double-Blind, Dose Titration Study of the Efficacy and Anticholinergic Side Effects of Transdermal Compared to Immediate Release Oral Oxybutynin Treatment of Patients with Urge Urinary Incontinence. *Journal of Urology*. 2001; 166: 140-145.

[8] Scientific Committee of the First International Consultation on Incontinence. Assessment and treatment of urinary incontinence. *Lancet*. 2000; 355; 2153-2158.

[9] Appell R et al. Prospective Randomized Controlled Trial of Extended-Release Oxybutynin Chloride and Tolterodine Tartrate in the Treatment of Overactive Bladder: Results of the OBJECT Study. *Mayo Clin Proc*. 2001; 76: 358-363.

[10] Millard R et al. Clinical Efficacy and Safety of Tolterodine Compared to Placebo in Detrusor Overactivity. *Journal of Urology*. 1999; 161: 1551-1555.

[11] Larsson G et al. Tolterodine in the Treatment of Overactive Bladder: Analysis of the Pooled Phase II Efficacy and Safety Data. *Urology*. 1998; 53: 990-998.

[12] Atan A et al. Tolterodine for Overactive Bladder: Time to Onset of Action, Preferred Dosage, and 9-month Follow-up. *Techniques in Urology*. 1999; 5 (2): 67-70.

- Dosing interval would be prolonged, leading to higher patient compliance and convenience
- Continuous delivery avoided the peaks which follow oral dosing
- First-pass metabolism would be avoided, leading to lower concentrations of the metabolite, N-desethyloxybutynin, which may attenuate the side-effects observed with oral dosing

Medical Officer's Comment

While N-desethyloxybutynin may be associated with dry mouth, it is also an active metabolite and may be responsible for some of the pharmacological activity of the drug.[13]

TheraTech opened the IND by submitting three first-in-man clinical studies: **O96004** and **O96005**, two dermatotoxicity studies (one with daily dosing for 14 days and one with a repeat insult design to evaluate for contact sensitization, each using the oxybutynin 5 cm^2 TDS (which contained 4.62 mg oxybutynin) in up to a total of 125 subjects and **O96003** a single-dose pharmacokinetic study comparing the — 13.1 mg/10 cm^2 oxybutynin transdermal system and an oral oxybutynin 5 mg tablet in 12 healthy volunteers. Jean Fourcroy, MD, PhD was the Medical Officer who reviewed N000.

During the clinical development program that resulted in the filing of the present NDA, the Sponsor had frequent interactions with the Division of Reproductive and Urologic Drug Products (DRUDP) via correspondence, meetings, and teleconferences. On February 18, 1997, the sponsor submitted a document specifying that — the composition of the drug product was changed (including the surface area) to include oxybutynin base 13.1 mg in a 13 cm^2 system (to deliver 4.4 mg in 4 days). A Guidance meeting was held on June 2, 1997 to discuss the Phase 2 protocol **O96017** and offer preliminary criteria for conducting phase 3 trials for urinary urge incontinence.

An end of Phase II meetings was held with DRUDP on November 10, 1999. Important information conveyed to the Sponsor at that meeting (based on the meeting minutes) included the following:

"a single efficacy and safety study may be sufficient to allow for NDA fileability and review; robustness of the data submitted to support the claim of efficacy and safety will determine approval; there is risk in performing fewer rather than more trials to support safety and efficacy"

— are not acceptable to support product efficacy or labeling and promotional claims"

"if the pharmacokinetics of the drug is shown to be similar to that of other approved formulations of oxybutynin, the data on 300 patients for six months would be satisfactory; however, the Division recommends data on use for 12 months on at least 50 patients given the chronic use of this class of drugs for this indication"

On December 10, 1999, Watson Pharmaceuticals, Inc. acquired TheraTech and the IND holder was changed to Watson Laboratories, Inc. (a subsidiary of Watson Pharmaceuticals, Inc.).

The protocol for the one pivotal Phase III study (Protocol O99009) were submitted to DRUDP for review on December 17, 1999 in N018. Norman S. Marks, MD was the Medical Officer who reviewed N018. Comments were conveyed to the sponsor in two regulatory letters (dated January 20, 2000 and February 8, 2000) and included the following:

"The completed study report should: a) Include subgroup analyses by age, gender and ethnicity for both safety and efficacy. B) Investigate the impact of missing data in the interpretation of study results."

[13] Yarker Y et al. Oxybutynin A Review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging*. 1995; 6 (3): 245.

"The results from the proposed analyses of quality of life data will be considered exploratory."

"The open-label, uncontrolled second phase [Week 12 through 24] of the study is satisfactory for gathering safety data but will not allow for any efficacy claims in subsequent labeling and promotion."

A pre-NDA meeting was held with DRUDP on December 8, 2000 to discuss 18 items. The pre-meeting package stated that Watson intended to only seek approval for the oxybutynin 39 cm^2 TDS. Important information conveyed to the sponsor at that meeting (based on the meeting minutes) included the following:

"In the submission, the sponsor should address the following issues:

- comparability of blood levels between the transdermal system and the oral formulation of oxybutynin
- absence of a dose response
- indicate the numeric changes from baseline to endpoint and compare between treatment groups; it is premature to comment on the treatment effect at this time
- indicate if there is any treatment by center interaction or any particular subgroup that succeeded more than others"

"the extent of exposure described for the 39 cm^2 patch (109 patients for 11-12 weeks and 43 patients for 19-20 weeks) may not be adequate"

"as stated at our End of Phase 2 meeting on November 10, 1999, DRUDP continues to recommend that the sponsor provide data on 300 patient for 6 months and 50 patients for one year (at the highest dose)."

"if the sponsor plans to seek approval for the [redacted] the 39 cm^2 transdermal patch, sufficient data should be submitted to support [redacted]

"the primary efficacy analyses and results of the study should be based on ITT population; ITT population should include all subjects randomized to the study; for subjects without any post baseline efficacy data, baseline value should be carried forward"

On March 29, 2001, the sponsor submitted to **IND 50,489** in N034 a new Phase 3 Protocol **O00011**, entitled "A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study Comparing Oxybutynin Transdermal Systems versus Tolterodine Long Acting Capsules in Patients with Overactive Bladder". It is comparing oxybutynin TDS 39 cm^2 versus over-encapsulated Detrol LA versus matching placebo transdermal systems and capsules during a 12-week treatment period in 360 patients at 40-50 US sites. George S. Benson, MD was the Medical Officer who reviewed N034. Comments were conveyed to the sponsor in a regulatory letter (dated April 20, 2001) and included the following:

1. Please define what you mean by "a beneficial response on current anticholinergic therapy."
2. The study population is enriched by including only patients who have benefited from prior anticholinergic therapy.
3. Please clarify whether or not both types of incontinence ("urge" or "stress") will be included in the primary efficacy endpoint. Note that the urinary diary requires that patients characterize their incontinent episode as either "urge" or "stress".
4. Note that the Division will consider both incontinence episodes and urinary frequency as "primary endpoints." If you elect to assess urinary frequency as a secondary endpoint, the

statistical analysis plan should be designed to evaluate both incontinence and urinary frequency.

5. The primary comparison for Oxybutynin Transdermal System will be oxybutynin versus placebo. All other comparisons are exploratory.

In addition, safety comparisons must be pre-specified and a statistical analysis plan for safety comparisons submitted.

3.3.2 Issues Arising during Clinical Trials

The prespecified Statistical Analysis Plan (SAP) for **O99009** was for a parametric ANCOVA analysis (i.e. means), however the sponsor primarily evaluated the data by non-parametric ranking procedure (i.e. medians) after it was noted that the distributional normality assumption failed to hold for the diary data.

After the last patient completed the double-blind period (Part 1) of Study **O99009**, the sponsor noted six patients were "misrandomized" (i.e. the treatment they received was not the treatment they had been randomized to) as follows:

Patient #	Randomized Treatment	Treatment Received
1422	39 cm^2	26 cm^2
1737	26 cm^2	39 cm^2
1743	39 cm^2	26 cm^2
2821	13 cm^2	39 cm^2
2902	13 cm^2	26 cm^2
2905	26 cm^2	13 cm^2

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ON ORIGINAL

The Statistical Analysis Plan was then changed to primarily analyze a modified intent to treat population (mITT) where each patient was grouped by the treatment actually received. It should be noted that the sponsor had been directed by DRUDP at the pre-NDA meeting to base the primary efficacy analysis on the intent to treat (ITT) population.

It was noted during DSI inspection of Site #03 (Dr. Joseph Antoci) for Study O99009 that efficacy and safety data were not correctly transcribed from the case report forms to the data set listings. The sponsor was asked to resolve the efficacy data discrepancies regarding the urinary diary data for Subjects #0304 and #0325 as follows:

> Subject #0304: Study records for urinary diary data reported by the subject on April 15, 2000 (Day 5 of endpoint week) were noted during site inspection; this data was not located in the NDA 21-351 data listing in Volume 70 for Subject #0304 at Visit 7 on pg. 106-109.
>
> Subject #0325: Baseline urinary diary data was reported in NDA 21-351 Volume 70 for Visit 3 on pg. 293-298 as having been obtained from February 21-27, 2000. However, study records indicate that the subject was rejected for randomization on February 28, 2000 because the subject did not complete Days 6 and 7 of the diary correctly. The subject repeated the screening diary between February 29 and March 7, 2000 and was approved for randomization on March 7, 2000. The baseline data collected between February 29 and March 7, 2000 was not located in the NDA 21-351 data listing in Volume 70 for Visit 3 on pg. 293-298.

In an amendment to the Original NDA dated February 28, 2002, the sponsor confirmed the two urinary diary data discrepancies and stated that they were due to transcription errors that occurred when copying the original diaries into the Case Report Forms (CRFs). It is the reviewer's opinion that if these two discrepancies were the only discrepancies, they would have little or no potential impact on the study results. However, the sponsor then conducted further investigations to explore the possible occurrence of these types of data entry discrepancies in other diaries and at other sites.

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In the same amendment to the Original NDA dated February 28, 2002, the sponsor stated that a total of 111 diaries contained fewer than 7 days of data, of which 80 diaries were "correct as entered (database and CRF diary records consistent)". They discovered that 21 diaries were provided to the Contract Research Organization (CRO) as double-sided copies and during the data entry process, it appeared that only one side of the page was entered. An additional 10 diaries were identified as having a total of 13 missing pages. The sponsor did not provide the visit numbers, the subject numbers, or the total number of missing pages for these 31 diaries. The sponsor states they are in the process of re-evaluating the efficacy data incorporating the data from missing urinary diary pages. Therefore, neither the potential nor the true effect on the study results from the missing efficacy data can be determined at this time.

Medical Officer's Comment

The reviewer rejects the sponsor's conclusion that these 31 diaries with missing pages would have a minimal impact on study income since they were distributed among all four treatment groups (i.e. 10 diaries with missing pages in the 13 cm^2 group, 4 in the 26 cm^2 group, 9 in the 26 cm^2 group, and 8 in the 39 cm^2 group). The efficacy data must be re-evaluated with the missing data to determine its impact.

In addition, the sponsor examined the data listings for the 87 subjects who repeated the baseline diaries and stated that for 4 subjects the second diary was not correctly used as the baseline.

Medical Officer's Comment

The reviewer rejects the sponsor conclusion that since approximately 2500 diaries were collected, the estimated error rate is approximately only 1-1.4%. A key issue is how many diaries were incorrect of the approximately 1000 baseline and last visit diaries, which was not provided.

It was noted during DSI inspection of Site #21 (Dr. Ira Klimberg) for Study O99009 that certain efficacy data on subjects #2105 and 2122 had not been obtained, however the investigator falsely stated that it had been obtained. A Form FDA 483 was issued.

A directed inspection at Site #12 (Dr. Brian Feagins) for Study O99009 revealed several serious regulatory violations, a Form FDA 483 was issued, and DSI recommended that Study O99009 data from this site not be used in support of the pending application.

Medical Officer's Comment

While the March 1, 2002 final DSI Clinical Inspection Summary does not comment on the "missing pages" from the 31 diaries nor on the 4 incorrect baseline diaries, this reviewer believes that these data discrepancies should be considered during regulatory review of this NDA. Ultimately, these discrepancies will require further clarification and efficacy results may need to be re-analyzed. This reviewer recommends any future Study O99009 re-analysis be conducted on the ITT population after deleting the data on subjects #2105 and 2122, deleting the data from Site #12, utilizing the second set of diaries if the baseline urinary diary was repeated, and utilizing the correctly transcribed urinary diary data.

3.4 Other Relevant Information

3.4.1 Related Submissions

Studies included in NDA 21-351 were conducted under IND 50,489.

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Related NDAs NDA 17-577 (Ditropan®-oxybutynin chloride 5 mg tablets)
NDA 18-211 (Ditropan®-oxybutynin chloride syrup 5 mg/5mL)
NDA 20-771 (Detrol®-tolterodine 1 and 2 mg tablets)
NDA 20-897 (Ditropan® XL, oxybutynin extended release 5, 10, 15 mg tablets)

Related INDs NDA 21-228 (Detrol® LA-tolterodine 2 and 4 mg extended release capsules)

3.4.2 Foreign Marketing Status

Oxybutynin transdermal systems are not marketed in any foreign country.

3.4.3 Other Pharmacologically Related Agents Under Study

4 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

4.1 Toxicology Review

The **Nonclinical Pharmacology and Toxicology** section of NDA 21-351 presented primary data from two dermal irritation and sensitization studies (RR95-0022 and RR95-0023), a series of nonclinical studies conducted in Japan summarized in Report A-2-1-3, and supporting relevant literature findings about oxybutynin.[14] The transdermal formulation of oxybutynin was not studied in the provided relevant literature, however the literature was presented to characterize the known pharmacology and toxicology of oxybutynin. No preclinical toxicology issues were reported by the primary toxicology reviewer (Dr. Alex Jordan) that are of particular relevance to this clinical review.

4.2 Clinical Pharmacology and Biopharmaceutics Review

The **Clinical Pharmacology** section of NDA 21-351 presented oxybutynin primary dermal irritation/sensitization data from two US clinical studies as follows:

Protocol	Total N (M:F)	Treatment	Duration of Treatment
O96004-Phase I, open label, skin irritation and cumulative irritation study, single site	29 (14:15)	5 cm^2 TDS placebo TDS	2 weeks: 14x One active TDS and 1 placebo TDS applied daily
O96005-Phase I, open label, skin irritation and sensitization study, single site	115 (43:72)	5 cm^2 TDS placebo TDS	3 weeks: 3x per week for 24 hours: 1 active and 1 placebo TDS; 24-hour challenge

[14] Report RR95-0022 is in Volume 8 on pg. 141-156, Report RR95-0023 is in Volume 8 beginning on pg. 157, and Report A-2-1-3 is in Volume 27 on pg. 1-139.

The **Human Pharmacokinetics and Bioavailability** section of NDA 21-351 presented oxybutynin primary pharmacokinetic data from four US clinical studies as follows:

Protocol	Total N (M:F)	Treatment	Duration of Treatment
O96003-Phase I, randomized, open label, single dose, 2-way crossover, single site	15 (7:8)	1) 10 cm^2 TDS 2) oxybutynin 5 mg oral tablet	1) 96 hours 2) Single tablet
O99005-Phase I randomized, open label, single dose, 2-way crossover, single site	18 (8:10)	1) 39 cm^2 TDS 2) oxybutynin 5 mg oral tablet	1) 96 hours 2) Single tablet
O99006-Phase I randomized, open label, single dose, 3-way crossover, single site	24 (11:13)	39 cm^2 TDS on: 1) abdomen 2) buttock 3) hip	**All 3 arms:** 96 hours per TDS application site with at least 7 days washout
O99007-Phase I randomized, open label, multiple dose, 3-way crossover, single site	26 (13:13)	1) 13 cm^2 TDS 2) 26 cm^2 TDS 3) 39 cm^2 TDS	**All 3 arms:** (2 x 84 hours 1 x 96 hours), 14-day washout

The **Clinical** section of NDA 21-351 presented oxybutynin primary pharmacokinetic data from two US clinical studies as follows:

Protocol	Total N (M:F)	Treatment	Duration of Treatment
O96017-Phase II randomized, double-blind, active controlled, two-arm, dose titration, 12 sites	76 (6:70)	1) 1, 2, 3, or 4 TDS 13 cm^2 twice weekly 2) oxybutynin oral tablets (2.5 mg bid, 5 mg bid, 5 mg tablets tid, or 7.5 mg tablets tid)	6 weeks: plasma oxybutynin and N-desethyloxybutynin concentrations drawn at baseline evaluation and at Treatment Days 13-14, 27-28, and 41-42.
O99009 Part I-Phase 3 randomized, double-blind, placebo controlled, four-arm, parallel, 40 sites	520 (42:478)	1) 13 cm^2 TDS + 26 cm^2 placebo TDS twice weekly 2) 26 cm^2 TDS + 13 cm^2 placebo TDS twice weekly 3) 13 cm^2 TDS + 26 cm^2 TDS twice weekly 4) 13 cm^2 placebo and 26 cm^2 placebo TDS twice weekly	12 weeks: plasma oxybutynin and N-desethyloxybutynin concentrations drawn at V_3 (end of baseline evaluation) and at V_5 (Week 6) and V_7 (Week 12) if subject was wearing at least one TDS
O99009 Part II-Phase 3 open label, dose-titration, three-arm, parallel, 40 sites	411 (35:376)	1) 13 cm^2 TDS twice weekly 2) 26 cm^2 TDS twice weekly 3) 13 cm^2 TDS + 26 cm^2 TDS twice weekly	12 weeks: plasma oxybutynin and N-desethyloxybutynin concentrations drawn at V_{10} (Week 12) if subject was wearing at least one TDS

The sponsor also provided summaries for eight completed studies (Vol. 27 pg. 1-139) conducted in Japan (one dermal irritation Phase I study and seven Phase I pharmacokinetic studies) and a tabular summary of an ongoing early Phase II clinical study (Vol. 28 pg. 13) in Japan (A2-0102).

According to the primary biopharmaceutical reviewer (Dr. Y. M. Choi), oxybutynin is delivered consistently during the wearing period for up to 4 days with delivery rate of 0.1 mg/cm^2/day, the delivery rate is proportional to the active surface size, steady state is reached after second application of oxybutynin TDS, demographic characteristics such as gender, age, and weight do not appear to significantly affect the pharmacokinetics of oxybutynin and N-desethyloxybutynin (DEO), and in the Phase 1 studies during the wearing period of 84-96 hours, 19 out of 329 application did not appropriately adhere to the application site. Of special concern to Dr. Choi was the substantially less systemic exposure (4-6 times less) to DEO following the application of oxybutynin 39 cm^2 TDS compared to Ditropan (oxybutynin) 5 mg tablet. Dr. Choi commented that since DEO is known to have equal pharmacological activity to oxybutynin, therefore "poor efficacy (sic)" as well as less adverse events, if any, may be due to the significantly less exposure to DEO.

Dr. Choi concluded that the clinical pharmacology and biopharmaceutics data in the human pharmacokinetics and biopharmaceutics section of NDA 21-351 is acceptable, provided the sponsor's appropriate responses to the Agency's comments on labeling changes at a later time.

Medical Officer's Comment

The medical reviewer concurs with the above findings and conclusion.

5 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1 Pharmacokinetics

In the literature, mean pharmacokinetic (PK) parameters of oral oxybutynin after administration of single 5 mg doses to healthy young adult volunteers and repeated 5 mg doses to elderly patients with urge incontinence and detrusor instability have been reported (Table 1). The literature oral oxybutynin PK parameters were compared to the oral and transdermal oxybutynin PK parameters reported in NDA 21-351 (Table 2).

Table 1. Literature Mean Oxybutynin Pharmacokinetic Parameters* (Standard errors not provided in article)

Parameter	Single dose healthy young volunteer (n=8)	Single dose healthy elderly (n=10)	Single dose frail elderly (n=10)	Multiple dose in healthy elderly (n=10) (dose 5 mg tid)	Multiple dose in frail elderly (n=10) (dose 5 mg bid)
C_{max} (µg/L)	13.4	16.7	32.0	18.1	37.3
T_{max} (h)	0.76	0.69	0.60	0.65	0.56
$T_{1/2}$ (h)	2.0	2.3	4.6	3.1	5.4
AUC (µg/L • h)	21.4	31.8	48.4	36.9	103.6

*Yarker Y et al. Oxybutynin A Review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging*. 1995: 6 (3): 251.

Table 2. NDA 21-351 Mean ± SD Oxybutynin Pharmacokinetic Parameters*

Protocol	Treatment	C_{max} (ng/mL)	T_{max} (hrs)	$AUC_{0-\infty}$ (ng • hr/mL)	$t_{1/2}$ (hrs)
O96003	10 cm^2 TDS (96 hours) oxybutynin 5 mg (single dose)	1.4 ± 0.3 8.3 ± 6.3	47.2 ± 30.3 0.7 ± 0.4	93 ±32 12.9 ± 8.2	Data not collected 0.7 ± 0.5
O96017	2 TDS 13 cm^2 3 TDS 13 cm^2 4 TDS 13 cm^2 oxybutynin 5 mg bid ** oxybutynin 5 mg tid ** oxybutynin 7.5 mg tid **	2.0 ± 1.1 3.3 ± 1.2 5.4 ± 2.3 2.7 ± 5.7 2.8 ± 2.3 4.5 ± 6.7	Data not collected		
O99005	39 cm^2 TDS (96 hours) oxybutynin 5 mg (single dose)	3.0 ± 0.8 7.4 ± 5.6	56.4 ± 34.9 0.8 ± 0.3	235 ± 58 13.2± 7.4	7.2 ± 1.8 1.3 ± 0.1
O99006	39 cm^2 TDS abdomen 39 cm^2 TDS buttock 39 cm^2 TDS hip	3.4 ± 1.1 4.0 ± 1.5 3.7 ± 1.3	44.5 ± 20.2 45.0 ± 16.3 43.6 + 19.4	279 ± 99 319 ± 128 308 ± 126	Data not collected
O99007	13 cm^2 TDS 26 cm^2 TDS 39 cm^2 TDS	2.3 ± 0.8 4.4 ± 1.3 6.6 + 2.4	20.3 ± 16.4*** 13.6 ± 9.5*** 17.9 ± 18.2***	143 ± 39 274 ± 59 408 ± 108	Data not collected
O99009 Part I	13 cm^2 TDS 26 cm^2 TDS 39 cm^2 TDS	1.2 ± 0.6 2.6 ± 1.4 3.9 ± 2.0	Data not collected		

*Compiled from Table 3.6-1 in Vol. 1 pg. 142

** Trough level taken immediately prior to first AM dose at steady state

***Oxybutynin TDS T_{max} was significantly less in multiple dose study O99007 than in other three trials when it was studied, probably due to differences in frequency of sampling.

Medical Officer's Comments:

1) **In Study O96017 the oxybutynin TDS group blood samples were drawn when maximum levels should have been reached (i.e. at 24-48 hours post TDS application), while the oral blood samples were drawn just prior to the AM dose when the lowest level should have been reached. It is not appropriate to compare the results of oral oxybutynin "trough" blood samples with transdermal oxybutynin "maximum" blood samples.**

2) **The mean oral and transdermal oxybutynin PK parameters obtained in NDA 21-351 varied significantly between the six clinical trials where it was evaluated, particularly the transdermal C_{max}, T_{max}, and AUC.**

3) **The mean oral oxybutynin PK parameters obtained in NDA 21-351 differed from the values reported in the literature, particularly regarding C_{max}, AUC, and $t_{1/2}$. Note: µg/L=ng/mL**

The overall oxybutynin delivery rate of 0.1 ± 0.02 per square centimeter of system surface area per day was derived from residual content analysis data from used systems. Plasma oxybutynin profiles after single-dose oxybutynin TDS administration demonstrated a short lag phase to establish transport through the stratum corneum followed by a gradual increase in plasma oxybutynin concentrations occurring during the initial 24-48 hours of system application, followed by a slow decline in concentrations over the remainder of the 96-hour wear period. Plasma oxybutynin profiles after multiple-dose oxybutynin TDS administrations demonstrated steady-state conditions were achieved approximately 24 hours after application of the first oxybutynin TDS. No accumulation was demonstrated. Mean plasma oxybutynin concentrations were generally somewhat higher in males than in females while D-desethyloxybutynin were generally higher in females. In O99007, dose proportionality was demonstrated over the range of system sizes studies (13 cm^2 to 39 cm^2).

Special Populations pharmacokinetic studies to evaluate the oxybutynin TDS in the elderly, in pediatric subjects, or in subjects with renal impairment, liver insufficiency, or other disease states were not performed. No drug-drug interaction studies were performed.

5.2 Bioavailability

The sponsor stated that oxybutynin AUC during the application of a single oxybutynin 39 cm^2 TDS for four days was approximately equal to one 5 mg oxybutynin tablet orally administered qid (four times a day)[15].

Medical Officer's Comments:

1) **It is unclear how the sponsor can support the above statement since transdermal oxybutynin is not bioequivalent to oral oxybutynin. In addition, only the AUC following the administration of a single oral oxybutynin 5mg tablet was determined in Protocols O96003 and O99005. The AUC should have been determined following administration of a 5 mg oral oxybutynin tablet qid for 4 days in order to compare to the AUC determined following wearing a transdermal oxybutynin 39 cm^2 TDS for 4 days (96 hours). The Clinical Pharmacology and Biopharmaceutics Reviewer, Dr. Y. Choi, modeled the oral oxybutynin single dose data and simulated the systemic exposure profile after multiple oral administration. He concluded that at steady state, a similar C_{max} (6.6ng/ml vs. 7.4 ng/ml) and larger AUC (408 vs. 224 ng.hr/min) of oxybutynin were predicted following application of TDS 3.9 mg/day system every 96 hours compared to those following oral administration of 5 mg Ditropan QID.**

2) **One could roughly estimate the AUC for oxybutynin 5 mg oral tablet administered qid for four days and then compare it to the AUC for a single 39 cm^2 TDS for four days from study O99005 as follows: if the AUC (ng • hr/mL) listed for the oxybutynin 5 mg tablet (13.2 ± 7.4) is multiplied x 4 (for four doses per day) and then multiplied again x 4 (for four days), the result is 211.2 ± 118.4 (i.e. range from 92.8 to 329.6). However even this rough estimate of oral oxybutynin AUC is not equivalent to the AUC (ng • hr/mL) listed for the 39 cm^2 TDS of 235 ± 58 (i.e. 177 to 293) due to the larger variability and standard deviation in the oxybutynin tablet data.**

3) **Due to the larger variability demonstrated in oral oxybutynin AUC, more patients taking oral oxybutynin may have higher (and more efficacious) AUC values than patients taking transdermal oxybutynin. It is unclear if efficacy with oral dosing is primarily seen in the subset of oral oxybutynin patients who demonstrate higher AUC values. If so, a lower mean AUC in the oral oxybutynin group may be associated with similar efficacy to a higher mean AUC in the transdermal oxybutynin group.**

The sponsor also stated that the oxybutynin AUC during application to the buttock and hip were bioequivalent to the abdomen.[15] The oxybutynin C_{max} following application to the buttock was 4 ng/ml compared to 3.7 ng/ml for the hip and 3.4 ng/mL for the abdomen in Protocol O99006.

Medical Officer's Comments:

The Office of Clinical Pharmacology and Biopharmaceutics Reviewer for NDA 21-351, Dr. Young Moon Choi, determined that the buttock and hip application sites for oxybutynin were bioequivalent to the reference abdominal application site based on the 90% confidence intervals (CI) based on the estimated ratios for oxybutynin C_{max}, $AUC_{0-\infty}$, and adjusted $AUC_{0-\infty}$, being within the acceptable range for bioequivalence (0.80, 1.25). However, DEO was produced about 20% higher after application of TDS on the buttock than on the abdomen. He concluded that this difference may not have a significant clinical impact, since the magnitude of the difference is insignificant compared to the extreme DEO exposure after oral administration of Ditropan.

[15] NDA 21-351 Vol. 1 pg. 141

6 DESCRIPTION OF CLINICAL DATA AND SOURCES

6.1 Clinical Data Submitted in Support of NDA 21-351

6.1.1 IND Clinical Trials

The clinical development of the oxybutynin TDS began in 1996. The sponsor submitted clinical data in NDA 21-351 from 8 studies, all conducted in the US under IND 50,489: **six Phase 1** studies (O96003, O96004, O96005, O99005, O99006, and O99007), **one Phase 2** study (O96017), **and one Phase 3** study (O99009).

6.1.2 NonIND Clinical Trials

Eight Phase 1 nonIND Japanese clinical trials were submitted as a tabular listing (Vol. 29 on pg. 11-12) and summarized in a report (Vol. 27 pg. 1-137). Only a tabular listing was submitted for the **one Phase 2** Japanese nonIND clinical trial, A2-0102 or 144-012 (Vol. 29 on pg.13).

6.1.3 Secondary Sources of Clinical Data

No postmarketing data were submitted in NDA 21-351 since oxybutynin TDS has not been marketed in any country to date. The Sponsor provided no published articles regarding the findings from the oxybutynin TDS clinical trials. A PubMed search by the reviewer revealed one article published on the **Phase 1** oxybutynin TDS Study **O99005**[16] and one article published on the **Phase 2** oxybutynin TDS Study **O96017**.[17] Both articles were reviewed.

6.2 Overview of Clinical Studies Included in the NDA

The sponsor submitted data from 2 primary clinical studies (**O96017** and **O99009**) to support the safety and efficacy of oxybutynin TDS. A brief description of these studies is provided below:

Protocol	Total N (M:F)	Treatment	Duration of Treatment
O96017-Phase 2 randomized, double-blind, active controlled, two-arm, dose titration, 12 sites	76 (6:70)	**1)** 1, 2, 3, or 4 TDS 13 cm^2 twice weekly (N=38) **2)** oxybutynin oral tablets: 2.5 mg bid, 5 mg bid, 5 mg tid, or 7.5 mg tablets tid (N=38)	6 weeks
O99009 Part I-Phase 3 randomized, double-blind, placebo controlled, four-arm, parallel, 40 sites	520 (42:478)	**1)** 13 cm^2 TDS + 26 cm^2 placebo TDS twice weekly (N=130) **2)** 26 cm^2 TDS + 13 cm^2 placebo TDS twice weekly (N=133) **3)** 13 cm^2 TDS + 26 cm^2 TDS twice weekly (N=125) **4)** 13 cm^2 placebo and 26 cm^2 placebo TDS twice weekly (N=132)	12 weeks

[16] Zobrist R et al. Pharmacokinetics of the R- and S-enantiomers of oxybutynin and N-desethyloxybutynin following oral and transdermal administration of the racemate in healthy volunteers. *Pharm Res.* 2001; 18 (7): 1029-34.

[17] Davila G et al. A Short-term, Multicenter, Randomized Double-blind Dose Titration Study of the Efficacy and Anticholinergic Side effects of Transdermal Compared to Immediate Release Oral Oxybutynin Treatment of Patients with Urge Urinary Incontinence. *Journal of Urology.* 2001; 166: 140-145.

O99009 Part II-Phase 3 open label, dose titration, 40 sites	411 (35:376)	1) 13 cm^2 TDS twice weekly (N=61) 2) 26 cm^2 TDS twice weekly (N=139) 3) 39 cm^2 TDS twice weekly (N=211)	12 weeks
O99009 Part III-Phase 3 safety extension, open label, three-arm, 10 sites	142 (12:130)	1) 13 cm^2 TDS twice weekly (N=13) 2) 26 cm^2 TDS twice weekly (N=54) 3) 39 cm^2 TDS twice weekly(N=75)	28 weeks

6.3 Patient Exposure to Oxybutynin Transdermal System

6.3.1 Exposure to Oxybutynin Transdermal System Through 1 Year

At the time of NDA submission, a total of 855[18] subjects had received one or more applications of oxybutynin TDS. Safety data was integrated into the safety report on 625 subjects studied in the US under **IND 50, 489**: 542 overactive bladder patients and 83 healthy volunteers. Study **O99009** 28-week safety extension period (Part III) data was not integrated in to the safety report, however it was submitted separately in the 120-day Safety Update Report on August 10, 2001. Data from 230 additional healthy volunteers were not integrated into the safety report: 144 healthy volunteers from 2 US dermal irritation studies (**O96004** and **O96005**) and 86 healthy volunteers from the 8 Japanese Phase 1 studies.

It should be noted that prolonged exposure to oxybutynin TDS only occurred during Protocol O99009. Per Table 14.3.5.1.4.3 in the 120-Day Safety Update Report Vol. 1 on pg. 460-463, a total of 149 patients were exposed to oxybutynin transdermal treatment at any dose for at least 26 weeks (i.e. at least 6 months) and 57 patients for at least 52 weeks (i.e. at least one year). In correspondence dated January 16, 2002, the sponsor clarified that 66 patients were actually exposed for at least 52 weeks to any dose of oxybutynin transdermal treatment. The 120-Safety Update Report Table 14.3.5.1.4.3 in Vol. 1 on pg. 461-462 states:

- 46 patients were exposed for at least 26 weeks (i.e. 6 months) to oxybutynin 26 cm^2 TDS
- 0 patients were exposed for at least 52 weeks (i.e. at least 1 year)) to oxybutynin 26 cm^2 TDS
- 64 patients were exposed for at least 26 weeks (i.e. 6 months) to oxybutynin 39 cm^2 TDS
- 1 patient was exposed for at least 52 weeks (i.e. 1 year) to oxybutynin 39 cm^2 TDS

It should be noted that the time interval of patient exposure by dose provided by the sponsor is for the total exposure to a particular dose that occurred at anytime during study **O99009** and should not be interpreted as the number of weeks of **continuous** exposure to a particular dose.

Medical Officer's Comments:

1) **The reviewer concurs with the sponsor that it was appropriate to exclude the additional 230 healthy volunteers from the integrated safety report. The subjects in the US dermal irritation studies were exposed to oxybutynin 5 cm^2 TDS, which was a significantly lower**

[18] Sponsor states in Vol. 1 on pg. 153 that 230 subjects participated in the 10 nonintegrated studies and in Vol. 1 on pg. 151 that 220 subjects participated in the 10 nonintegrated studies. Per reviewer assessment of the Tabular Listings of Clinical Studies in Vol. 28 on pg. 5-22, 230 subjects participated in the 10 nonintegrated studies.

dose than administered to patients in the integrated studies. The reviewer concurs that it was appropriate to exclude the 8 Japanese Phase I oxybutynin studies from the integrated safety report since only study summaries were provided.

2) The sponsor has submitted limited safety data regarding patients exposed for prolonged periods to the — doses of oxybutynin 26 and 39 cm^2 TDS. During the pre-NDA meeting on December 8, 2000, it was recommended that the sponsor "provide data on 300 patients for 6 months and 50 patients for one year (at the highest dose)". The sponsor did not fulfill this recommendation: data on 64 patients for 6 months and 1 patient for one year (at the highest dose) was provided.

3) The reviewer considers safety data collected when a subject was exposed to any particular dose or higher dose of oxybutynin to be the primary safety data to support approval of that particular dose. The reviewer considers safety data collected when a subject was exposed to less than any particular dose of oxybutynin to be secondary safety data regarding supporting approval of that particular dose.

6.3.2 Exposure to Oxybutynin Transdermal System Beyond 1 Year

All exposures for beyond one year occurred in Protocol O99009. Per Table 14.3.5.1.4.2 and Table 14.3.5.1.4.3 in 120-Day Safety Update Report Vol. 1 on pg. 456-463, 57 patients were exposed to treatment at any dose for at least 52 weeks, 17 for at least 53 weeks, 11 for at least 54 weeks, and 8 for at least 55 weeks, 4 for at least 56 weeks, 3 for at least 58 weeks, 2 for at least 59 weeks, and 1 for at least 60 weeks.

7 CLINICAL REVIEW METHODS

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7.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

- Original NDA 21-351 (correspondence date April 26, 2001; date received April 26, 2001)
  - Volumes 1, 29-140
  - Electronic case report forms (CRFs) and case report tabulations (CRTs)
- 120-Day Safety Update Report (correspondence date August 10, 2001; date received August 13, 2001)
  - Volumes 1-15
- Submission correspondence dated June 27, 2001 (BM-minor clinical amendment- response to request for information including list of investigators in Phase 3 trial)
- Submission correspondence dated August 3, 2001 (BI-minor microbiology amendment)
- Submission correspondence dated September 4, 2001 (BZ-minor multidisciplinary amendment- request for partial waiver and deferral of pediatric studies)
- Submission correspondence dated September 27, 2001 (BM-minor clinical amendment- response to request for information regarding adhesion data and human diagram in the Patient Information Insert)
- Submission correspondence dated October 23, 2001 (US-FDA initiated action with no status change- one regulatory letter granting partial waiver for pediatric studies and not granting request for a deferral of pediatric studies)
- Submission correspondence dated October 23, 2001 (US-FDA initiated action with no status change-one regulatory information request letter)

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- Submission correspondence dated December 12, 2001 (PU-Submission of Draft Pediatric protocol and Response to FDA Comments)
- Submission correspondence dated January 16, 2002 (BM-Response to Request for Information from Medical Officer regarding extent of oxybutynin TDS exposure)
- Submission correspondence dated February 28, 2002 (BM-Response to Request for Information regarding DSI inspection of Site #03 revealing efficacy data discrepancies)
- NDA 21-351 Microbiology Review #1 to HFD-580 from Office of New Drug Chemistry Microbiology Staff/HFD-805 dated August 30, 2001
- NDA 21-351 Microbiology Review #2 to HFD-580 from Office of New Drug Chemistry Microbiology Staff/HFD-805 dated October 11, 2001 regarding NDA 21-351 Submission BI (correspondence date August 3, 2001)
- Five Annual Reports for IND 50, 489 (correspondence dates: June 19, 1997; October 23, 1998; September 30, 1999; October 17, 2000; and July 27, 2001)
- Minutes of all regulatory meetings and telephone conferences with Sponsor that were contained in Division Document Room, Division files, and Division Filing System (DFS)

The 120-Day Safety Update Report of August 10, 2001 contained updated information for the safety extension (Part III) for clinical trial O99009. Information contained in the Safety Update is presented and discussed in the relevant sections of this review.

7.2 Review Processes and Procedures

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7.2.1 Materials Reviewed

The review conducted by this medical officer focused on the principal controlled and randomized primary efficacy study (Study O99009-Part I), the supporting controlled and randomized secondary efficacy study (Study O96017), and the primary safety study (Study O99009-Part II dose titration and Part III safety extension). All materials submitted in paper format for these studies were considered during the conduct of this review. Reviews of supplemental studies O96004 and O96005 dermal irritation and sensitization studies focused on safety issues. Pharmacokinetic data pertinent to proposed labeling from the US Studies O96003, O99005, O99006, and O99007 was reviewed. The adhesion data was reviewed by the Clinical Pharmacology and Biopharmaceutics reviewer, Dr. Choi.

7.2.2 Safety and Efficacy Reviews

The accuracy of the Sponsor's primary efficacy analyses (based on the data listings provided by the Sponsor) was reviewed by Sue-Jane Wang, Ph. D, FDA Senior Mathematical Statistician (see separate statistical review). In addition, the medical reviewer prepared separate supplemental safety tabulations based on the sponsor's submitted data.

7.3 Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits. The Division of Scientific investigation selected three study centers (Sites # 03, 21, and 23) that participated in Study O99009 for audit. One additional study center (Site #12) was audited as a "for cause" inspection.

The audit of Dr. Joseph Antoci (Site #03) at Urology Specialists, PC in Waterbury Connecticut involved reviewing the records for all 23 enrolled patients. No regulatory violations were noted, however discrepancies between source data for 13 different patients and the data listings that the sponsor submitted to DSI for use in the inspection was noted. In twelve patients, a total of two serious adverse events (SAE) and 27 non-serious adverse events (AE) were reported to the sponsor on case report forms but were not included in the sponsor's data listing submitted to DSI.

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Medical Officer's Comments

The two SAEs and 24 of the 27 AEs discrepancies were resolved upon review: they occurred during Study O99009 safety extension (Part III) and were reported in the 120-Day Safety Update Report dated August 10, 2001. It is the opinion of the reviewer that the three remaining AE discrepancies were not significant discrepancies.

Data discrepancies regarding the urinary diary data were noted in two patients by DSI as follows:

Subject #0304: Urinary diary data reported by the subject on April 15, 2000 (Day 5 of endpoint week) was not captured in the sponsor's data listing submitted to DSI. All of the April 15, 2000 diary entries pertain to normal voids (total of ten) experienced by the subject after awakening at 7:50am; there are no post-bedtime entries noted.

Subject #0325: Baseline urinary diary data is reported in the sponsor's data listing as having been obtained from February 21-27, 2000. However, study records indicate that the subject was rejected for randomization on February 28, 2000, because the subject did no complete Days 6 and 7 of the diary correctly. The subject repeated the screening diary between February 29 and March 7, 2000 and was approved for randomization on March 7, 2000. The baseline data collected between February 29 and March 7, 2000 was not included in the sponsor data listing provided for the inspection.

Medical Officer's Comments

No explanation for the urinary diary data discrepancies was identified at the clinical site by DSI or by the Medical Officer upon review of data listings in NDA 21-351 (as submitted for Subject #0304 in Volume 70 for Visit 7 on pg. 106-109 and for Subject # 0325 in Volume 70 for Visit 3 on pg. 293-298). In the February 11, 2002 e-mail, the sponsor was asked to resolve the discrepancies. The sponsor's response, submitted as NDA Original Amendment (BM) dated February 28, 2002, confirmed the two urinary diary data discrepancies. It is the reviewer's opinion that if these two discrepancies were the only discrepancies, they would have little or no potential impact on the study results. However, the response discusses that the sponsor conducted further investigations to explore the possible occurrence of these types of data entry discrepancies in other diaries.

The sponsor stated that a total of 111 diaries contained fewer than 7 days of data, of which 80 diaries were "correct as entered (database and CRF diary records consistent)". They discovered that 21 diaries were provided to [redacted] as double-sided copies and during the data entry process, it appeared that only one side of the page was entered. An additional 10 diaries were identified as having a total of 13 missing pages. The sponsor did not provide the visit numbers, the subject numbers, or the total number of missing pages for these 31 diaries. The sponsor states they are in the process of re-evaluating the efficacy data incorporating the data from missing urinary diary pages. Therefore, neither the potential nor the true effect on the study results from the missing efficacy data can not be determined at this time. The reviewer rejects the sponsor's conclusion that these 31 diaries with missing pages would have a minimal impact on study income since they were distributed among all four treatment groups (i.e. 10 diaries with missing pages in the 13 cm^2 group, 4 in the 26 cm^2 group, 9 in the 26 cm^2 group, and 8 in the 39 cm^2 group) since the efficacy data must be re-evaluated with the missing data to determine its impact.

In addition, the sponsor examined the data listings for the 87 subjects who repeated the baseline diaries and for 4 subjects the second diary was not correctly used as the baseline.

The reviewer rejects the sponsor conclusion that since approximately 2500 diaries were collected, the estimated error rate is approximately only 1-1.4%. The key issue is how many diaries were incorrect of the approximately 1000 baseline and last visit diaries, which was not provided.

At Dr. Antoci's site:

- 23 patients entered and 20 patients completed the double-blind portion (Part I)[19]
- 19 patients entered and 18 completed the open-label dose titration period (Part II)[20]
- 14 patients entered and 11 completed the open-label safety extension (Part III)[21]

The audit of **Dr. Ira W. Klimberg (Site #21)** at The Urology Center in Ocala, Florida involved reviewing the records for nine subjects. A Form 483 was issued for two protocol violations. Subjects 2105 and 2122 were enrolled despite not meeting inclusion criteria; they lacked documentation of urinary void volume during two days of the 7-day baseline urinary diaries and the Visit 3 case report forms for these subjects erroneously indicated that the subjects a) successfully completed the 7-day urinary diaries; and b) recorded in these diaries the volume voided during two consecutive days. The data appeared acceptable. At Dr. Klimberg's site:

- 23 patients enrolled and 18 patients completed the double-blind portion of the study (Part I)[22]
- 18 patients entered and 13 completed the open-label dose titration period (Part II)[23]
- 11 patients entered and 8 completed the open-label safety extension (Part III)[24]

The audit of **Dr. Robert Michael Kroeger (Site #23)** at the Nebraska Clinical Research Center in Omaha, Nebraska involved reviewing the records for 12 patients. No regulatory violations were noted and the data appeared acceptable. At Dr. Kroeger's site:

- 18 patients enrolled and 16 completed the double-blind portion (Part I)[25]
- 10 patient entered and 8 completed the open-label dose titration period (Part II)[26]
- 3 patients entered and 3 completed the open-label safety extension (Part III)[27]

The results of the "for cause" inspection of **Dr. Brian Authur Feagins** (Site #12) at Urology Specialists & Associates in Dallas, Texas revealed several serious regulatory violations and a Form FDA 483 was issued for record keeping inadequacies/inaccuracies pertaining to both hard copy and electronic records, which included misrepresented data for two patients. At Dr. Feagin's site:

- 14 patients were enrolled and 10 completed the double-blind period (Part I)[28]
- 10 patients entered and 9 completed the open-label dose titration period (Part II)[29]
- Patients in Dr. Feagin's site did not participate in the open-label safety extension (Part III)

The sponsor submitted the double-blind treatment period (mITT cohort) data with and without Dr. Feagins site.[30] DSI recommended that the Study O99009 data from Dr. Feagin's site not be used in support of the NDA. Thus the data for Study O99009 was reanalyzed without Dr. Feagin's data. This reanalysis was performed by Sue-Jane Wang, Ph. D., Senior Mathematical Statistician, and in her review she noted that when excluding Site #12, a statistically significant treatment effect of 39 cm^2

[19] Audit report and Table 14.1.1.1.1 in Vol. 46 on pg. 11
[20] Table 14.1.1.2.1 in Vol. 46 on pg. 25
[21] The audit report does not discuss the open label safety extension (Part III), however per Table 14.1.1.3.1 in the 120-Day Safety Update Report in Vol. 1 on pg. 60-61
[22] Table 14.1.1.1.1 in Vol. 46 on pg. 17
[23] Table 14.1.1.2.1. in Vol. 46 on pg. 29-30
[24] Table 14.1.1.3.1 in the 120-Day Safety Update Report in Vol. 1 on pg. 60-61
[25] Audit report
[26] Table 14.1.1.2.1 in Vol. 46 on pg. 30
[27] Table 14.1.1.3.1 in the 120-Day Safety Update Report in Vol. 1 on pg. 60-61
[28] Table 14.1.1.1.1 in Vol. 46 on pg. 14
[29] Table 14.1.1.2.1 in Vol. 46 on pg. 27
[30] With Site #12 in Tables 14.2.1.1.1-14.2.1.1.4.2 on pg. 74-84 and without Site #12 in Tables 14.2.1.1.5.1-Table14.2.1.1.5.4.2 in Vol. 46 on pg.85-92.

TDS using the non-parametric approach (i.e. median) was still obtained for the primary endpoint of urinary incontinence, but not when using the parametric (i.e. mean) approach. However, when excluding Site #12, a statistically significant treatment effect of 39 cm^2 TDS using the non-parametric and parametric was not obtained for the secondary endpoint of urinary frequency.

Financial disclosure statements. The sponsor submitted financial disclosure statements for Investigators who participated in Study O99009. These financial disclosure documents were reviewed by Jeanine Best, M.S.N., R.N., Regulatory Project Manager in the Division of Reproductive and Urologic Drug Products (HFD-580). In O99009, there were 199 principal and subinvestigators (investigators) at 40 sites. Financial disclosure was received for all investigators and none had any disclosable information. Ms. Best concluded in her review that there was no disclosure of financial interests that could bias the outcome of Trial O99009 in NDA 21-351.

Central Laboratory. In O99009, the central laboratory utilized for laboratory testing of safety parameters was [redacted] In O99009, plasma samples were assayed for oxybutynin and N-desethyloxybutynin at [redacted]

Site Monitoring. [redacted] was responsible in O99009 for monitoring sites, handling serious adverse event reports, maintaining the clinical trial database, auditing the clinical laboratory, performing statistical analyses according to their standard operating procedures, data validation. The final study report was prepared by the [redacted] located at [redacted] The sponsor stated, "On-site monitoring visits were performed throughout the study to ensure site compliance with the protocol and CRF completion requirements" (Vol. 45 on pg. 41).

Medical Officer's Comments

- [redacted] are a well known, qualified clinical laboratory and a Contract Research Organization, respectively. Both are widely used by the pharmaceutical industry to conduct and/or monitor drug clinical trials.
- Assay validation procedures and quality control at [redacted] are addressed and reviewed in the Biopharmaceutical Review by Y. M. Choi, PhD. The Biopharmaceutical Reviewer identified no areas of concern.

8 INTEGRATED REVIEW OF EFFICACY (PRIMARY CLINICAL STUDIES)

8.1 Efficacy Assessments

8.1.1 Primary Efficacy Endpoints and Assessments

In the pivotal Phase III study **O99009**, the primary efficacy assessment in the double-blind period was the change from baseline (Visit 3) to endpoint (Visit 7 [Week 12] or last observation carried forward [LOCF]) in the number of incontinence episodes per week recorded in the 7-day urinary diary by patients receiving active treatment versus those receiving placebo.

In the Phase II study **096017**, the primary efficacy assessment was a "responder analysis" of the change in the number of incontinence episodes in order to evaluate for equivalence in efficacy of the oxybutynin TDS versus oral oxybutynin.

8.1.2 Secondary Efficacy Endpoints and Assessments

In study **O99009**, secondary efficacy assessments included the continuous efficacy variables of mean number of urinary incontinence episodes, the mean changes in the average daily frequency, the average urinary volume, and the visual analog scale (VAS) global assessment of disease state. Quality of life measures also served as secondary efficacy assessments.

In study **O96017**, response to treatment in secondary endpoints were evaluated as the change from baseline to endpoint. The secondary endpoint assessments included analogue scores for incontinence, volume to first contraction, and maximum cystometric capacity.

8.1.3 Overview of Statistical Analyses for Primary and Secondary Efficacy Endpoints

Statistical issues are discussed in detail in the separate Statistical Review by Sue-Jane Wang, Ph. D., Senior Mathematical Statistician. A brief overview of the most important statistical analyses is presented in this Section. No interim analyses were planned. For study **O99009**, the Statistical Analysis Plan (SAP) was finalized on March 2, 2000 and was amended on August 10, 2000 to reflect Protocol Amendment #2 dated May 24, 2000, which added the 28-week safety extension period. The sponsor stated in e-mail correspondence dated January 16, 2001 that the SAP was also amended on August 10, 2000 to change the primary analysis population from the intent to treat (ITT) to the modified intent to treat (mITT) population. The number of urinary incontinence episodes, the daily urinary frequency, the urinary volume per void, and the Global Assessment of Disease States were treated as continuous variables.

8.1.3.1 Primary Efficacy Endpoints

Primary analysis. In **O99009**, the primary efficacy analysis population was planned to be the intent to treat (ITT) population, which included all patients who received at least one dose of study medication and had at least one efficacy assessment after the first dose. Because 6 patients were correctly randomized, however received the incorrect treatment during the double-blind period, the sponsor opted to amend the SAP on August 10, 2000 (after the last patient had completed the double-blind period-Part I) by changing the primary efficacy analysis population to a modified intent to treat (mITT) cohort, where the patients were grouped by the treatment actually received. DRUDP had not agreed to this change in the SAP. The missing data were completed using last observation carried forward (LOCF). The number of urinary incontinence episodes were obtained from the 7-day urinary diary and were normalized to seven days for patients with less than seven days of recorded data.

In **O96017**, the primary statistical analysis was to evaluate for efficacy equivalence between transdermal and oral oxybutynin. Patients who completed at least 4 weeks of treatment with oxybutynin were considered evaluable for efficacy. Responders were patients with >30% decrease from baseline to endpoint in the number of daily incontinence episodes during treatment. A 95% confidence interval for the difference in proportion of responders between treatments was constructed by using a normal distribution approximation with estimates of standard errors based on observed proportions

Secondary analyses. In **O99009**, the secondary efficacy analysis population was the evaluable cohort, which was planned to include all patients who met the inclusion and exclusion criteria for the study, were without significant protocol violation(s), and who completed at least nine weeks of double-blind treatment. However, the sponsor changed the definition of the evaluable cohort to include all patients who met the inclusion and exclusion criteria for the study, were without significant protocol deviations, **except misrandomization**, and completed at least nine weeks of double-blind treatment. In **O96017**, the secondary efficacy analysis population was the intent to treat population.

Medical Officer's Comments

- **The Original Protocol O99009 dated November 22, 1999 stated that the primary efficacy analysis population was to be the intent-to-treat (ITT) cohort. Neither Amendment #1 and #2 to Protocol O99009 changed the primary efficacy analysis population to a modified intent to treat cohort. DRUDP did not agree with this change in the primary analysis population for Study O99009. It is unclear if the August 10, 2000 revised statistical plan making this change in the primary efficacy analysis population was submitted to IND 50,489. The annual report for IND 50,489 dated October 17, 2000 does not list the revised statistical plan as being submitted in an amendment.**

8.1.3.2 Secondary Efficacy Endpoints

In O99009, the secondary efficacy endpoint analysis compared the mean change in average daily urinary frequency and the mean change in average urinary volume per void from baseline to the end of the double-blind period using LOCF imputation for patients not completing the double-blind period. An additional secondary efficacy endpoint analysis compared the mean change from baseline to end of the double-blind treatment period in the Global Assessment of Disease State.

In O96017, a comparison of the change from baseline to endpoint in the secondary variables between transdermal and oral oxybutynin treatments was performed using two-sample, two-sided t-tests for continuous variables and Wilcoxon rank sum tests for ordinal variables.

8.2 Primary Clinical Study to Support Efficacy Claim: Study O99009

8.2.1 Overall Design

The Phase III, multicenter Study O99009 entitled "Transdermal Oxybutynin in Patients with Urge Urinary Incontinence: A 12-Week Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study with a 12-Week Open-label, Dose-Titration, Safety Period and a 28-Week Open-Label Safety Extension" was the primary clinical study conducted by the sponsor to support the efficacy of Oxytrol™. The original protocol dated November 22, 1999 consisted of a screening period of 2 to 4 weeks duration followed by two treatment periods: a placebo-controlled, 4-arm, randomized (1:1:1:1 ratio), double-blind, fixed-dosing, 12-week treatment period (Part I), followed by an optional, 12-week, open-label, dose-titration period (Part II). In Amendment #2 dated May 24, 2000, an additional treatment period was added: an optional 28-week open-label safety extension treatment period (Part III) for approximately 150 patients from the sites with the highest enrollment.

Patients with overactive bladder exhibiting symptoms of urge urinary incontinence and urinary frequency were enrolled. During the screening period, bladder and fluid management training for treatment-naïve patients OR a 2-week washout period from current pharmacological treatment took place. This was followed by a baseline evaluation involving a 7-day urinary diary and a 2-day voided volume and, if necessary, an additional 1-week period to repeat the 7-day urinary diary and 2-day voided volume. During the initial treatment period, transdermal systems (TDS) of one of three dose levels of Oxytrol™ (13 cm^2, 26 cm^2, or 39 cm^2) or placebo were applied twice a week to the abdomen. During the double-blind treatment period (Part I), all patients applied two TDS, one each of the 13 cm^2 and 26 cm^2 sizes, in specified combinations of placebo and active TDS. Seven-day urinary diaries and 2-day voided volumes were collected prior to the Week 3, Week 6, Week 9 and Week 12 Visits during the double-blind treatment period (Part I). During the open-label treatment period (Part II), all patients began by applying a single oxybutynin 13 cm^2 TDS. The investigators could then titrate the patient's dose during the first four weeks of the open-label period (Part II). The dose remained fixed for the last eight weeks of the open-label period (Part II). Seven-day urinary diaries and 2-day voided volumes were collected prior to the Week 12 Visit during the open-label treatment period (Part II). During the safety extension treatment period (Part III), all patients continued treatment with a single oxybutynin 13 cm^2, 26 cm^2, or 39 cm^2 TDS at the same dose as was

administered for the final 8 weeks of the open-label treatment period (Part II). Urinary diary and volume voided data was not collected during the safety extension period (Part III).

It was planned that 450 patients would enter the trial from 40 sites with 400 patients being evaluable for efficacy and 300 patients completing 24 weeks of active treatment (Part I and Part II). Amendment #2 stated that 150 patients from the highest enrollment sites were planned to enter the safety extension period (Part III) to ensure one-year exposure to oxybutynin TDS in approximately 100 patients.

Medical Officer's Comments

- **The study design utilized for Study O99009 prevented ¼ of the patients from being exposed for one-year to oxybutynin, since they were treated with placebo during the initial double-blind treatment period (Part I). The reviewer notes that the sponsor extended the safety extension treatment period (Part III) for selected patients longer than 28 weeks without amending the protocol.**
- **The study design for the open-label parts permitted patients to switch among the three dose levels. This switching resulted in few patients having continuous exposure for one year at the doses sought for regulatory approval.**

8.2.2 Patients

For Study O99009, patients with a history of overactive bladder with symptoms of urgency, urge urinary incontinence, and urinary frequency were enrolled if they met the following inclusion and exclusion criteria.

Inclusion Criteria

Each patient must comply with the following criteria:

- The patient is a male or a non-pregnant, non-lactating female using adequate means of birth control if of childbearing potential.
- The patient is at least 18 years of age.
- The patient has a history of overactive bladder with symptoms of urgency, urge urinary incontinence, and urinary frequency, with or without neurological disease.
- The patients recorded ≥10 urge urinary incontinent episodes and ≥56 voids in the 7-day baseline urinary diary during the washout period.
- The patient's average recorded urinary void volume was ≤350 mL per void during two days of the 7-day baseline urinary diary.
- The patient has pure urge or mixed urinary incontinence with a predominance of urge incontinence episodes.
- The patient has a post-void residual volume of ≤250 mL, as measured by ultrasound or catherization.
- The patient is capable of understanding and complying with the protocol and has signed the informed consent document.

Exclusion Criteria

Patients meeting any of the following criteria will be excluded form the study:

- The patient did not complete all seven days of the 7-day urinary diary during the screening period.

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- The patient has a history of lower urinary tract surgery within the past six months.
- The patient has any relevant deviation from normal in physical examination, ECG, or clinical laboratory test results, as evaluated and documented by the investigator. Patients with clinically significant abnormalities indicative of previously undiagnosed medical disease should be referred for follow-up treatment.
- The patient has a history of alcohol/drug abuse within the past year.
- The patient has a known hypersensitivity to oxybutynin or related compounds.
- The patient has a history of hypersensitivity to transdermal medications.
- The patient has an active skin disorder, such as eczema, seborrhea, or psoriasis.
- The patient has known narrow angle glaucoma or exhibits a shallow anterior chamber upon physical examination.
- The patient has one or more conditions that may cause urinary incontinence or urgency, such as urinary tract infection, requirement for acute or intermittent use of diuretics, or excessive use of alcohol. [Note: Patients with evidence of acute urinary tract infection may be referred for treatment and then be re-evaluated for entry into the study.]
- The patient has a diagnosis of interstitial cystitis, urethral syndrome, or painful bladder syndrome.
- The patient has a PSA >4ng/mL, or a history of prostate biopsy positive for prostate carcinoma. Patients with PSA≤10 ng/mL and documented negative prostate biopsies within one year prior to study entry are acceptable. [Note: Patients who have undergone a prostate biopsy within 3 months may not enter the study.]
- The patient has a history of significant medical problems that may confound the outcome of this study (e.g., >3 urinary tract infections within the past 12 months, unstable diabetes mellitus, anticipated changes in hormonal status [patients receiving hormone treatments must maintain the same hormone treatment regimen throughout the study period]).
- The patient has a diagnosis of overflow incontinence secondary to underactive or acontractile detrusor or outlet obstruction or other evidence of significant outlet obstruction.
- The patient uses concomitant medications that may affect detrusor activity, including anticholinergic agents, (e.g., propantheline, dicyclomine, flavoxate, hyoscyamine) and tricyclic antidepressants (e.g., imipramine, doxepin, desipramine, nortriptyline).
- The patient has excessive consumption of caffeine (>5 cups of coffee, tea, or cola daily).
- The patient cannot maintain his or her usual program of nonpharmacologic management of incontinence (e.g., pelvic floor exercise, timed voiding/bladder training) during the study, if applicable.
- The patient has participated in another investigational drug study within 30 days prior to the first dose of transdermal oxybutynin or placebo.
- The patient is judged by the investigator to be unsuitable for enrollment in this study for any reason.

Medical Officer's Comments

- **Overall, these inclusion/exclusion criteria are considered appropriate.**
- **The post-void residual urine inclusion criteria of <250 mL is larger than in other similar clinical trials.**

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- **The Protocol O99009 inclusion criteria of at least 10 urinary incontinence episodes per week was greater than the number of baseline incontinence episodes in most controlled clinical trials for this indication.**

8.2.3 Study Drugs

8.2.3.1 Dose Selection

During the double-blind period (Part I), transdermal systems (TDS) of one of three dose levels of Oxytrol™ (13 cm^2, 26 cm^2, or 39 cm^2) or placebo were applied twice a week to the abdomen. Patients in each arm applied two TDS, one each of the 13 cm^2 and 26 cm^2 sizes, in a combination of placebo and active TDS as follows:

- Patients randomized to 13 cm^2 applied one active 13 cm^2 TDS and one placebo 26 cm^2 TDS
- Patients randomized to 26 cm^2 applied one placebo 13 cm^2 TDS and one active 26 cm^2 TDS
- Patients randomized to 39 cm^2 applied one active 13 cm^2 TDS and one active 26 cm^2 TDS
- Patients randomized to placebo applied one placebo 13 cm^2 TDS and one placebo 26 cm^2 TDS

During the open-label period (Part II), all patients began with the oxybutynin 13 cm^2 TDS. The investigators could titrate the patient's dose during the first four weeks of the open-label period (Part II). The dose remained fixed for the last eight weeks of the open-label period (Part II) and throughout the safety extension (Part III).

Medical Officer's Comment

It was accepted by the primary biopharmaceutical reviewer (Dr. Y. M. Choi), that oxybutynin is delivered consistently during the wearing period for up to 4 days with delivery rate of 0.1 mg/cm^2/day. Therefore the dose delivered with oxybutynin 13 cm^2 TDS is accepted as 1.3 mg/day, the dose delivered with oxybutynin 26 cm^2 TDS is accepted as 2.6 mg/day, and the dose delivered with oxybutynin 39 cm^2 TDS is accepted as 3.9 mg/day.

8.2.3.2 Choice of Comparator

A placebo control was deemed ethical and was used as in other overactive bladder trials.

8.2.3.3 Assignment to Study Drug

No stratification occurred prior to randomization. Patients were randomly assigned to one of three Oxytrol™ treatment doses or placebo in a 1:1:1:1 ratio according to a random assignment schedule prepared by a statistician at — prior to the start of the study with each block containing four subjects. Protocol O99009 stated that the randomization numbers were consecutive beginning with 8001 and patients were randomized to treatment in sequential order according to drug shipment (i.e. 8001-8008, 8009-8016, etc.).[31]

8.2.4 Study Procedures and Conduct

8.2.4.1 Schedule of Study Assessments

The original study **Schedule of Events** for Study **O99009** is presented in Table 3.

During the screening period and enrollment period, the subject came for three clinic visits (Visit 1-3). During **Visit 1**, consent was obtained, and a medical history, vital signs, and medication use history was obtained. Treatment-naïve patients were educated on bladder function, bladder control, and fluid management that may result in improvement in urinary incontinence. Patients on current pharmacological treatment for incontinence were withdrawn and began a two-week washout period During **Visit 2**, patients were trained on diary completion, collection and measuring of their urine,

[31] NDA 21-351 Vol. 50 pg. 61

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and how to distinguish between urge and stress incontinence episodes. Fasting blood samples for hematology, chemistries and serum PSA (men only), urine samples for urinalysis and for pregnancy testing (female patients of child-bearing potential only), 12-lead electrocardiogram (ECG) with a 1 minute rhythm strip, and vital signs were obtained. During **Visit 3**, the urinary diary was reviewed. Patients who failed to meet the urinary diary criteria or who failed to accurately complete the diary could be allowed to repeat (one time) the diary evaluation at the discretion of the investigator. After meeting the urinary diary requirement, the post-void residual volume (PVR) and vital signs were measured, a physical examination to include a genitourinary exam and 12-lead ECG with 1 minute rhythm strip was performed, concomitant medications were reviewed, the patient's Global Assessment of Disease State questionnaire and three QoL questionnaires (SF36, IIQ, and UDI) were completed, blood was collected for oxybutynin and N-desethyloxybutynin, patient eligibility for the study was determined according to the inclusion and exclusion criteria, and the patient was randomized and instructed on the proper use of TDS. The systems were to be applied every 3.5 days to provide a twice-weekly regimen (ex. Monday mornings and Thursday evenings) on an area of skin free of scars, cuts, erythema, edema, pustules, and excessive hair, on the abdomen, and on a site where clothing will not interfere with proper adhesion. Systems which fell off during the study were to be replaced with a new system of the same size at the same site. Subjects were advised that normal activities were allowed during the study periods, however strenuous activities such as jogging, tennis, swimming, and aerobics may result in loss of transdermal system adhesion.

During the randomized, double blind, placebo-controlled treatment period (Part I), the subject came in for four visits (**Visits 4 to 7**). During each of these four visits (**Visit 4 to 7**), concurrent medications were recorded, diary records were collected, reviewed, and transcribed, vital signs were obtained, compliance was reviewed, adverse events were monitored, skin tolerability at TDS application site and adhesion of current TDS was assessed, and any significant changes in fluid intake or non-pharmacological incontinence management were evaluated. At only **Visit 5** and at **Visit 7**, the UDI and IIQ QoL questionnaires were completed and blood samples for measurement of plasma concentrations of oxybutynin and N-desethyloxybutynin were collected. At only **Visit 7**, the SF-36 QoL questionnaire and a Global Assessment of Disease State using a visual analog scale (VAS) were completed, a physical exam including a genitourinary exam, a 12-lead ECG, and a PVR measurement were performed, and fasting blood for hematology and chemistry and urine samples for urinalysis and urine beta-HCG (only for females of child-bearing potential) were obtained.

At each visit (**Visits 8 to 10**) during the optional, open-label, dose titration extension period (Part II), concurrent medications were recorded, vital signs were obtained, compliance was reviewed, adverse events were monitored, skin tolerability at TDS application site and adhesion of current TDS was assessed, and any significant changes in fluid intake or non-pharmacological incontinence management were evaluated. Dosage adjustments were made at **Visit 8** and **Visit 9** only. At only **Visit 10**, a Global Assessment of Disease State using a visual analog scale (VAS) and the SF-36. UDI, and IIQ QoL questionnaires were completed, diary records were collected, reviewed, and transcribed, a physical exam including a genitourinary exam, a 12-lead ECG, and a PVR measurement were performed, fasting blood for hematology and chemistry and urine samples for urinalysis and urine beta-HCG (only for females of child-bearing potential) were obtained, and blood samples for plasma concentrations of oxybutynin and N-desethyloxybutynin were collected if the subject was wearing at least one system.

Table 3. Study O99009 Original Schedule of Events

Assessments	Screening Period			Treatment Period							
	Initial Evaluation	Washout	Start of Baseline Evaluation	End of Baseline Evaluations	Double-Blind				Open-Label		
					Weeks (days)						
					3	6	9	12	2	4	12
Study Days	-22	-21 to -9	-8 to -2	0 to 1	2 to 21	22 to 42	43 to 63	64 to 84	1 to 14	15 to 28	29 to 84
Patient Visits	V_1		V_2	V_3	V_4	V_5	V_6	V_7	V_8	V_9	V_{10}
Informed Consent	X										
Medical History	X										
Physical Examination				X				X			X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X	X
Urinalysis			X					X			X
ECG				X[4]				X			X
Serum Chemistries (fasting)			X					X			X
CBC			X					X			X
PSA (males only)			X								
Urine beta-HCG[1]			X					X			X
7-day Urinary Diary[2]			X		X	X	X	X			X
2-Day Voided Voume[3]			X		X	X	X	X			X
PVR				X				X			X
QoL questionnaires											
• SF-36				X				X			X
• UDI & IIQ				X		X		X			X
Global Assessment				X				X			X
Plasma Concentration				X		X		X			X
Study Drug Dispensed				X	X	X	X	X	X	X	
Skin Tolerability Assessment					X	X	X	X	X	X	X
Adhesion Assessment					X	X	X	X	X	X	X
AE Assessment					X	X	X	X	X	X	X

[1] Urine beta-HCG test were only performed on female patients of childbearing potential
[2] A 7-day urinary diary (consecutive days)was recorded during the week immediately prior to the indicated visit beginning at least eight days prior to the visit.
[3] For 2 consecutive days of the 7-day diary, patients were required to collect all urine during normal voids and record the voided volume on the diary card.
[4] Baseline ECG with a 1-minute rhythm strip was performed at either Visit 2 or Visit 3

The Original Schedule of Events was amended to add a safety extension (Part III) with **Visit 11** and **Visit 12** (see Table 4).

Table 4: Study O99009 (Part III) Safety Extension Schedule of Events

Assessments	Treatment Period	
	Extension	
	Weeks *(days)*	
	14	28
Days	*1 to 98*	*99 to 196*
Patient Visits	V_{11}	V_{12}
Physical Examination		X
Concomitant Medications	X	X
Vital Signs	X	X
Urinalysis		X
ECG		X
Serum Chemistries (fasting)		X
CBC		X
Urine beta-HCG[4]		X
Study Drug Dispensed	X	
Skin Tolerability Assessment	X	X
Adhesion Assessment	X	X
AE Assessment	X	X

8.2.4.2 Key Efficacy Assessments

Key measurements for efficacy assessments included:

- Change from baseline to last visit in the double-blind period in the number of urinary incontinence episodes recorded in the 7-day urinary diary (primary endpoint)
- Mean change from baseline to last visit in the double-blind period in the average daily urinary frequency (average daily urinary frequency was calculated by dividing the total number of events recorded on the 7-day urinary diary by the total number of days with data recorded in the diary)
- Mean change from baseline to last visit in the double-blind period in the average urinary volume per void (average urinary volume per void was calculated by dividing the sum of the voided volumes by the total number of voids recorded during the two consecutive day urine volume documentation)
- Mean change from baseline to last visit in the double-blind period in the Global Assessment of Disease State

8.2.4.3 Pharmacokinetic Assessments

Blood was collected for plasma concentrations of oxybutynin and N-desethyloxybutynin at Visits 3 (prior to beginning active treatment to confirm washout) and at Visits 5, 7, and 10 (only if the subject was wearing at least one TDS). Specimens were stored at the site until completion of the double-blind period of the study and then shipped via overnight courier to Watson Laboratories, Inc-Utah in a sufficient amount of dry ice to keep the tubes frozen for two days.

8.2.4.4 Withdrawal Criteria

In the protocol, it was stated that a patient might withdraw from the study if the patient experienced serious or unexpected adverse events/intercurrent illnesses. If these occurred, the patient was to undergo a detailed history, physical examination, and blood and urine samples for biochemistry,

hematology, urinalysis, and plasma concentrations of oxybutynin and N-desethyloxybutynin were to be collected. A patient might also withdraw if clinically significant hematological or biochemical changes from the initial values developed, if symptoms or conditions listed in the exclusion criteria developed during the course of the study, if the patient was noncompliant or in violation of the protocol, if the patient developed an intercurrent illness requiring prohibited medication (any medication that may affect detrusor activity, including anticholinergic agents such a propantheline, dicyclomine, flavoxate, hyoscyamine or tricyclic antidepressants such as imipramine, doxepin, desipramine, nortripyline), if the patient refused or was unable to participate further, or if the investigator considered withdrawal to be in the best interest of the patient. When a patient was withdrawn from the study (regardless of cause), all evaluations required at the scheduled study termination Visit were to be performed.

8.2.5 Results

8.2.5.1 Patient Disposition, Demographics, and Baseline Characteristics

A total of 1129 patients were screened for participation in Study **O99009**. The primary reason for screen failure was patient decision not to participate (175 patients), followed by failure to meet the required number of incontinence episodes (130 patients). A total of 520 patients (safety cohort) were randomized into the double blind period (Part I) at 40 US sites, with each site randomizing between 5 to 24 patients. Of the 447 patients who completed Part I (86% of the 520 enrolled patients) and were eligible to continue into the open-label safety period (Part II), 411 patients (91.9 % of the patients who completed Part I) entered Part II. Of the 411 patients who entered Part II, when they completed Part II:

- 61 patients (14.8%) had been titrated to oxybutynin 13 cm^2 TDS
- 139 patients (33.8%) had been titrated to oxybutynin 26 cm^2 TDS
- 211 patients (51.3%) had been titrated to oxybutynin 39 cm^2 TDS

Of the 358 patients who completed Part II, 142 entered the 28-week safety extension period (Part III). A total of 115 patients completed Part III. The primary reasons for patient withdrawal from treatment was adverse events (the rate varied in the three parts of the study from 7% to 10%), followed by patient decision to terminate (the rate varied in the three parts of the study from 1.5% to 9.2%). The first patient enrolled in Part I on December 21, 1999, in Part II on April 11, 2000, and in Part III on July 5, 2000. The last patient completed Part I on July 26, 2000, Part II on October 9, 2000, and Part III on April 19, 2001.

Baseline demographic characteristics for each of the 4 treatment arms in the double-blind period (safety cohort) of Study O99009 are summarized in Table 5. The majority of patients were Caucasian (89-94%). Mean treatment group ages ranged from 59.4 to 61.9 years, while individual ages ranged from 20 to 88 years. Median treatment group weights ranged from 162.5 to 180 pounds while individual weights ranged from 96 to 400 pounds. Mean duration of incontinence at entry was 109.7 months (9.1 years) $\pm$109 months and ranged from 5 to 780 months.

Table 5. **Study O99009 Double Blind Period (Part I) Demographics and Baseline Disease Characteristics***

	Overall N = 520	Oxybutynin TDS			Placebo N = 132 n (%)
		13 cm^2 N = 130	26 cm^2 N = 133	39 cm^2 N = 125	
Gender					
Female [n(%)]	478 (91.9%)	120 (92.3%)	123 (92.5%)	114 (91.2%)	121 (91.7%)
Male [n(%)]	42 (8.1%)	10 (7.7%)	10 (7.5%)	11 (8.8%)	11 (8.3%)
Race/Ethnicity					
Caucasian [n(%)]	473 (91%)	119 (91.5%)	118 (88.7%)	118 (94.4%)	118 (89.4%)
Black [n(%)]	31 (6%)	7 (5.4%)	10 (7.5%)	3 (2.4%)	11 (8.3%)
Hispanic [n(%)]	12 (2.3%)	3 (2.3%)	4 (3%)	2 (1.6%)	3 (2.3%)
Asian [n(%)]	4 (0.8%)	1 (0.8%)	1 (0.8%)	2 (1.6%)	0 (0%)
Age (yr.)					
Mean ± SD (range)	61.4 ± 13.3 (20-88)	61.5 ± 11.8 (28-87)	61.9 ± 13.5 (26-84)	59.4 ± 14.5 (20-86)	62.7 ± 13.1 (30-88)
Weight (lb)					
Median (range)	170 (96 - 400)	169.5 (113 – 400)	162.5 (96 - 316)	170 (102 - 300)	180 (103 – 339.5)
Duration of incontinence (months)					
Mean ± SD (range)	110.8 ± 113.8 (5-780)	109.3 ± 123.5 (6-780)	106.3 ± 105.3 (5-600)	118.4 ± 117.7 (6-564)	109.7 ± 109 (6-600)

*Safety cohort population; Table derived from Table 14.1.2.1.2 in Vol. 46 on pg. 39 and Table 11.2-1 in Vol. 45 on pg. 65

Medical Officer's Comments

- **The treatment groups within study O99009 were generally well balanced in terms of both demographics and baseline disease characteristics.**
- **It is unclear why less patients were enrolled in the oxybutynin 39 cm^2 group than in the other 3 groups (i.e. 5 less patients than the 13 cm^2 group, 7 less patients than the placebo group, and 8 less patients than the 26 cm^2 group). It was anticipated that randomization would result in more equal numbers of subjects in the 4 groups.**

8.2.5.2 Primary Efficacy Analyses and Endpoint

The planned primary efficacy analysis population per Original Protocol **O99009** as well as per Amendments #1 and #2 was the intent to treat (ITT) cohort, as defined as all patients, grouped by the actual treatment received, who received at least one application of a TDS system and provided data for at least one efficacy assessment after the first dose. However after the last patient had completed the double-blind treatment period (Part I), the primary efficacy analysis population was changed on August 10, 2000 to a modified intent-to-treat **(mITT)** cohort, which was defined as all patients, **grouped by the actual treatment received, who received at least one application of a TDS system** and provided data for at least one efficacy assessment after the first dose. Five of the 520 patients in the safety cohort did not have an efficacy assessment, so the mITT cohort for the double blind period (Part 1) included 515 patients. After the last patient completed the double-blind period (Part 1) of Study **O99009**, the sponsor noted that six patients in the double blind period (Part 1) ITT cohort were "misrandomized" (i.e. the treatment they received was not the treatment they had been randomized to), so the mITT cohort grouped those six patients into the treatment actual received. The secondary

efficacy analysis population was the evaluable cohort, which was defined as including all patients in the mITT cohort who met the inclusion and exclusion criteria, who were without significant protocol deviations(s) other than misrandomization, and who completed at least nine weeks of double blind treatment.

Medical Officer's Comments

- **The six patients entered into Study O99009 Part I who were misrandomized were Subjects #1422, 1737, 1743, 2821, 2902, and 2905[32] On 2/14/02, sponsor provided the following listing of the misrandomized patients, the treatment they had been randomized to, and the treatment actually received:**

Patient #	Randomized Treatment	Treatment Received
1422	39 cm^2	26 cm^2
1737	26 cm^2	39 cm^2
1743	39 cm^2	26 cm^2
2821	13 cm^2	39 cm^2
2902	13 cm^2	26 cm^2
2905	26 cm^2	13 cm^2

- **The Statistical reviewer analyzed the data using the ITT of the treatment actually assigned, labeled in her review as the rITT group, with the conclusion that the results of statistical significance were in general consistent between the sponsor's mITT cohort and this reviewer's as randomized analyses (rITT).[33] In addition, the Statistical reviewer stated that O99009 appeared to be underpowered for the observed treatment effect.[34]**

8.2.5.2.1 Change in number of urinary incontinence episodes from baseline to Week 12 in modified intent-to-treat (mITT) cohort

The baseline primary efficacy variable was well matched in the four treatment arms with a mean of 34.9-38.2 incontinence episodes per week (Table 14.2.1.1.1.1 in Vol. 46 on pg. 74). However all treatment arms had a very wide range of 2 to 163 incontinence episodes per week.

At the end point of the double-blind period (LOCF), there was a **mean** change from baseline of -19.2 $\pm$ 21.1 (placebo), -18.1 $\pm$ 19.5 (13 cm^2), -17.2 $\pm$ 18.3 (26 cm^2), and -21.7 $\pm$ 17.8 (39 cm^2) incontinence episodes per week with large standard deviations (Table 14.2.1.1.1.1 in Vol. 46 on pg. 75). At end point of double blind period (LOCF), there was a **median** change from baseline of -14.5 (placebo), -15.0 (13 cm^2), -14.0 (26 cm^2), and -19.0 (39 cm^2) incontinence episodes per week.

During the double blind period (Part I), patients in the mITT cohort treated with the 13 and 26 cm^2 oxybutynin TDS did **not** significantly change the **mean** number nor the **median** number of urinary incontinence episodes per week when compared with placebo. During the double blind period, patients in the mITT cohort treated with the 39 cm^2 oxybutynin TDS did **not** significantly change the **mean** number of urinary incontinence episodes per week when compared with placebo (p=0.2831). After the p-value was adjusted for multiple comparisons with the Dunnett's test, the 39 cm^2 oxybutynin TDS cohort experienced a statistically significant decrease in the **median** number of urinary incontinence episodes per week from baseline to endpoint (p=0.0165) compared with placebo. After deleting Site #12 from the analysis and adjusting the p-value for multiple comparisons with the Dunnett's test, this statistically significant median difference from placebo was maintained

[32] NDA 21-351 Vol. 67 Listing 16.2.3.1.1 on pg. 40-46
[33] Wang S. NDA 21-351 Statistical Review and Evaluation. pg. 6
[34] Wang S. NDA 21-351 Statistical Review and Evaluation. pg. 9

(p=0.0235). The **median** number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week compared with the median decrease of 14.5 (48.3%) episodes per week in the placebo group. A **median** statistically significant treatment effect for the oxybutynin 39 cm^2 TDS group was noted after 3 weeks of treatment (Visit 4) and was sustained throughout all subsequent visits in the double blind period (Table 14.2.1.1.1.1 in Vol. 46 on pg. 74-75 and Table 14.2.1.1.5.1 in Vol. 46 on pg. 85-86).

Table 6: Study O99009 Double Blind Period (Part I) Number of Urinary Incontinence Episodes (mITT population)*

	Placebo		Oxybutynin TDS 13 cm^2		Oxybutynin TDS 26 cm^2		Oxybutynin TDS 39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Number of urinary incontinence episodes per week								
Baseline (Visit 3)								
Mean and SD	37.7	23.98	38.2	26.23	36.2	22.81	34.9	18.43
Median	30.0		31.0		30.0		31.0	
Endpoint change from baseline								
Mean and SD	-19.2	21.14	-18.1	19.47	-17.2	18.32	-21.7	17.76
Median	-14.5		-15.0		-14.0		-19.0	
P-value[1] (Medians)			0.9992		1.0000		0.0165	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

* Table 14.2.1.1.1.1 in Vol. 46 on pg. 74-75; Listing 16.2.7.1.1

It is pertinent to compare Table 6 with the same data in Table 7 for the ITT population (labeled as the rITT in the Statistical Review) and in Table 8 for the mITT population excluding Site #12).

Table 7: Study O99009 Double Blind Period (Part I) Number of Urinary Incontinence Episodes (ITT population)*

	Placebo		Oxybutynin TDS 13 cm^2		Oxybutynin TDS 26 cm^2		Oxybutynin TDS 39 cm^2	
	n = 130		n = 131		n = 130		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Number of urinary incontinence episodes per week								
Baseline (Visit 3)								
Mean and SD	37.7	23.98	38.5	26.04	35.7	22.99	35.0	18.40
Median	30.0		31.0		30.0		31.0	
Endpoint change from baseline (LOCF)								
Mean and SD	-19.2	21.14	-18.5	19.63	-16.9	18.39	-21.6	17.48
Median	-14.5		-16.0		-14.0		-19.0	
P-value[1] (Medians)			0.9877		0.9931		0.0153	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

*Taken from Table 14.2.1.0.1 in Vol. 46 on pg. 66-67

Table 8: Study O99009 Double Blind Period (Part I) Number of Urinary Incontinence Episodes (mITT population excluding site #12)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Number of urinary incontinence episodes per week								
Baseline (Visit 3)								
Mean and SD	37.8	24.11	38.3	26.47	36.0	22.78	34.3	18.23
Median	30.0		31.0		30.0		31.0	
Endpoint change from baseline								
Mean and SD	-19.2	21.33	-18.3	19.59	-17.0	18.43	-21.0	17.08
Median	-14.0		-15.0		-14.0		-19.0	
P-value[1] (Medians)			0.9895		0.9995		0.0235	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

*Taken from Table 14.2.1.1.5.1 in Vol. 46 on pg. 85-86

The sponsor analyzed the results for an exploratory endpoint, "complete continence". The sponsor stated (Vol. 45 on pg. 72) that "complete continence" was achieved in 45 patients during the double-blind period: 10 in the **placebo** group, 12 in the **13 cm^2** group, 7 in the **26 cm^2** group, and 16 in the **39 cm^2** group (per Listing 16.2.7.1.1 in Vol. 68 on pg. 308-497). The sponsor did not specify if this was "complete continence" at the final visit during the double-blind period, or at anytime during the double-blind period. The reviewer analyzed Listing 16.2.7.1.1 and obtained the following results:

"Complete continence" was achieved in **49** patients at the endpoint of the double-blind period:

- **11** in the **placebo** group: Subjects # 0710, 1417, 1507, 1814, 2107, 2303, 2331, 2408, 2705, 3510 and 4002
- **12** in the **13 cm^2** group: Subjects # 0312, 0619, 0715, 2118, 2417, 3007, 3316, 3404, 3423, 3533, 3818, and 3922
- **8** in the **26 cm^2** group: Subjects # 0112, 0630, 1018, 1309, 1532, 2409, 3320, and 3521
- **18** in the **39 cm^2** group: Subjects # 0121, 0306, 0318, 0907, 1111, 1204, 1213, 1913, 2001, 2016, 2102, 2115, 2121, 2411(note: no baseline diary data in listing for patient #2411), 2821, 2911, 2923, and 3308

Medical Officer's Comments

- **Statistically significant benefit was not noted in the 13 cm^2 or 26 cm^2 groups.**
- **Statistically significant benefit was noted in the 39cm^2 group when medians were compared.**
- **This reviewer believes that in the oxybutynin 39 cm^2 TDS group, the median improvement with treatment compared to placebo of 0.64 urinary incontinence episodes per day, or equivalently 4.5 episodes per 7 days, is a small treatment effect.**
- **This reviewer believes it is relevant to provide data to the reader regarding the treatment effect of other anticholinergics for overactive bladder in other trials. For example, the difference at Week 12 between Detrol LA capsules (4 mg daily) and placebo during the Phase 3 registration trial was a mean improvement of 0.685 urinary incontinence episodes per day, or equivalently 4.8 urinary incontinence episodes per 7 days, compared to**

placebo. This mean treatment difference compared to placebo is significantly greater than the mean treatment difference of 2.5 urinary incontinence episodes per 7 days (0.357 episodes per day) seen with oxybutynin TDS 39 cm^2 in O99009.

- **The reviewer acknowledges that there are inherent problems in cross comparing data from NDAs. Reasons for bias include problems in differences in study populations, study design, and study procedures.**
- **Almost 10% of the patients in O99009 with any efficacy data (49 of 515) achieved "complete continence" (that is, no incontinence episodes at all) by the end of the double-blind period (Part I). It is unclear if these extreme responders are skewing the results for the primary efficacy endpoint.**
- **Eighteen patients who achieved complete continence by the end of the double blind period were clustered at five sites: 3 of 23 subjects at Site #03, 5 of 23 subjects at Site #21, 4 of 12 subjects at Site # 24, 3 of 12 subjects at Site #33, and 3 of 15 subjects at Site #35. Absent these results, the evidence of efficacy would be even poorer.**

8.2.5.2.2 Change in number of urinary incontinence episodes from baseline to Week 12 in Evaluable cohort

The baseline primary efficacy variable (Table 14.2.2.1.1.1 in Vol. 46 on pg. 98) was well matched in the four treatment arms with a mean of 36.7-38.0 incontinence episodes per week. However all treatment arms had a very wide range of 7 to 136 episodes of incontinence per week. At the end point of the double blind period (LOCF), there was a **mean** change from baseline of -18.6 $\pm$ 19.8 (placebo), -18.9 $\pm$ 20.0 (13 cm2), -17.6 $\pm$ 17.6 (26 cm^2), and -22.6 $\pm$ 18.44 (39 cm^2) incontinence episodes per week with large standard deviations (Table 14.2.2.1.1.1 in Vol. 46 on pg. 99). At end point of double blind period (LOCF), there was a **median** change from baseline of –14.0 (placebo), -15.0 (13 cm2), -15.0 (26 cm2), and -20.0 (39 cm^2) incontinence episodes per week. During the double blind period, patients in the evaluable cohort treated with the 13 and 26 cm^2 oxybutynin TDS did not change the **mean** number nor the **median** number of urinary incontinence episodes per week significantly differently from placebo. During the double blind period, patients in the evaluable cohort treated with the 39 cm^2 oxybutynin TDS did not change the **mean** number of urinary incontinence episodes per week significantly differently from placebo. The 39 cm^2 oxybutynin TDS evaluable cohort experienced a statistically significant decrease in the **median** number of urinary incontinence episodes per week from baseline to endpoint (p=0.0149) compared with placebo. The **median** number of incontinence episodes in the 39 cm^2 group decreased by 20 (54.1%) episodes per week compared with the **median** decrease of 14 (37.6%) episodes per week in the placebo group. This median improvement compared to placebo is 0.857 episodes per day or equivalently 6 episodes per 7 days.

A **median** statistically significant treatment effect was noted after 3 weeks of treatment (Visit 4) and was sustained throughout all subsequent visits in the double blind period (Table 14.2.2.1.1.1 in Vol. 46 on pg. 98-99).

Medical Officer's Comment

- **The primary endpoint efficacy in the evaluable cohort was consistent with the mITT cohort results.**

8.2.5.3 Secondary Efficacy Analyses and Endpoints

8.2.5.3.1. Mean change in average daily urinary frequency from baseline to Week 12 in mITT cohort

The baseline secondary efficacy variable of average daily urinary frequency was well matched in the four treatment arms with a mean of 11.8-12.4 urinations per day (Table 14.2.1.1.2.1 in Vol. 46 on pg. 77). However all treatment arms had a wide range of 8 to 29 urinations per day. At the end point of the double-blind period (LOCF), there was a **mean** change from baseline of -1.7 ± 2.95 (placebo), -1.8 ± 2.63 (13 cm^2), -1.8 ± 2.37 (26 cm^2), and –2.3 ± 2.48 (39 cm^2) urinations per day with standard deviations noted (Table 14.2.1.1.2.1 in Vol. 46 on pg. 78). At the end point of the double-blind period (LOCF), there was a **median** change from baseline of -1.0 (placebo), -2.0 (13 cm^2), -2.0 (26 cm^2), and -2.0 (39 cm^2) urinations per day. During the double blind period, patients in the mITT cohort treated with the 13 and 26 cm^2 oxybutynin TDS did **not** significantly change the **mean** number nor the **median** number of urinations per day when compared with placebo. During the double blind period, patients in the mITT cohort treated with the 39 cm^2 oxybutynin TDS did **not** significantly change the **mean** number of urinations per day when compared with placebo. The 39 cm^2 oxybutynin TDS cohort experienced a decrease in the **median** number of urinations per day from baseline to endpoint (p=0.0457) compared with placebo, however after data from Site #12 was removed from the mITT analyses, p=0.0529 and no statistical significance was demonstrated (Table 14.2.1.1.5.2 in Vol. 46 on pg. 87-88). The **median** number of urinations per day in the oxybutynin 39 cm^2 group decreased by 2 urinations per day compared with the median decrease of 1 urination per day in the placebo group.

Table 9: Study O99009 Double Blind Period (Part I) Average Daily Urinary Frequency (mITT population)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Daily urinary frequency (episodes)								
Baseline (Visit 3)								
Mean and SD	12.4	3.50	12.4	3.71	11.8	2.79	11.8	3.10
Median	11.0		11.0		11.0		11.0	
Endpoint change from baseline (LOCF)								
Mean and SD	-1.7	2.95	-1.8	2.63	-1.8	2.37	-2.3	2.48
Median	-1.0		-2.0		-2.0		-2.0	
P-value[1]			0.8292		0.3624		0.0457	

[1]P-value derived from Dunnett's test; Comparison significant if p < 0.05; Active treatment vs. placebo

* Table 14.2.1.1.2.1 in Vol. 46 on pg. 77-78; Listing 16.2.7.1.1

It is pertinent to compare Table 9 with the same data in Table 10 for the ITT population (labeled as the rITT in the Statistical Review) and in Table 11 for the mITT population excluding Site #12, since statistical significance is not reached for any treatment group in any population when adjustment for multiple comparisons is performed.

Table 10: Study O99009 Double Blind Period (Part I) Average Daily Urinary Frequency (ITT population)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 131		n = 130		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Daily urinary frequency (episodes)								
Baseline (Visit 3)								
Mean and SD	12.4	3.50	12.4	3.72	11.8	2.80	11.8	3.08
Median	11.0		11.0		11.0		11.0	
Endpoint change from baseline								
Mean and SD	-1.7	2.95	-1.8	2.62	-1.7	2.37	-2.3	2.48
Median	-1.0		-2.0		-2.0		-2.0	
P-value[1]			0.7926		0.4480		0.0366	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

* Table 14.2.1.0.2; in Vol. 46 on pg. 68-69

Table 11: Study O99009 Double Blind Period (Part I) Average Daily Urinary Frequency (mITT population excluding Site #12)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Daily urinary frequency (episodes)								
Baseline (Visit 3)								
Mean and SD	12.3	3.52	12.5	3.75	11.8	2.82	11.8	3.08
Median	11.0		11.0		11.0		11.0	
Endpoint change from baseline								
Mean and SD	-1.7	2.97	-1.9	2.63	-1.7	2.37	-2.2	2.44
Median	-1.0		-2.0		-2.0		-2.0	
P-value[1]			0.6799		0.4334		0.0529	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

* Table 14.2.1.1.5.2 in Vol. 46 on pg. 87-88.

A **median** statistically significant treatment effect compared to placebo was **not** noted at any Visit for the 39 cm^2 treatment group (Table 14.2.1.1.2.1 in Vol. 46 on pg. 77-78).

Medical Officer's Comments

- **It is clinically quite significant that when Site #12 is removed from the mITT population, no statistically significant improvement from baseline in the average daily urinary frequency occurred in any treatment arm when compared to placebo in any population since approximately 50% of overactive bladder patients have the symptom of urinary frequency without urinary incontinence.**

- **A median improvement with treatment compared to placebo of 1 less urination per day is of unclear clinical significance.**
- **It was noted that all three treatment groups demonstrated the same median change from baseline to endpoint of treatment compared to placebo (1 less urinations per day).**
- **At Visit 7 (Week 12), the average daily urinary frequency for the 39 cm^2 treatment group was mean –2.2 (SD 2.48) and median –2.0 in n=105 and when compared to placebo the p-value was 0.3231. When data from 17 additional patients, who had terminated earlier than Week 12, was added to the Visit 7 data, the average daily urinary frequency for the 39 cm^2 treatment group was only increased to mean –2.3 (SD 2.48), median was still –2.0 in n=123, however when compared to placebo the p-value changed to 0.0457. It is unclear why the marked difference between the Visit 7 (Week 12) data and endpoint double blind (LOCF) results occurred only in the 39 cm^2 treatment group. This result could have occurred if several patients who discontinued prematurely demonstrated a dramatic improvement in urinary frequency before discontinuing.**

8.2.5.3.2 Mean change in average urinary volume per void from baseline to Week 12

The baseline secondary efficacy variable of average urinary volume (mL) per void was well matched in the four treatment arms with a mean of 156.4-175.2 mL per void (Table 14.2.1.1.3.1 in Vol. 46 on pg. 80). However the treatment arms had a wide baseline range of 6 to 400 mL per void. At the end point of the double blind period (LOCF), there was a **mean** increase from baseline of 12.8 ± 59.05 (placebo), 8.8 ± 67.64 (13 cm^2), 25.1 ± 58.01 (26 cm^2), and 31.8 ± 67.56 (39 cm^2) mL per void with large standard deviations (Table 14.2.1.1.3.1 in Vol. 46 on pg. 81). At the end point of the double-blind period (LOCF), there was a **median** increase from baseline of 6.0 (placebo), 5.0 (13 cm^2), 19.0 (26 cm^2), and 24.0 (39 cm^2) mL per void. During the double blind period, patients in the mITT cohort treated with the 13 cm^2 oxybutynin TDS did **not** significantly change the **mean** urinary volume voided nor the **median** urinary volume voided when compared with placebo. During the double blind period, patients in the mITT cohort treated with the 26 and 39 cm^2 oxybutynin TDS did experience a statistically significantly increase in the **median** mL per void from baseline to endpoint when compared with placebo: p=0.0219 for the 26 cm^2 oxybutynin TDS cohort and p=0.0063 for the 39 cm^2 oxybutynin TDS cohort. The **median** increase from baseline in the average urinary volume (mL) per void in the 39 cm^2 group was 24 mL, in the 26 cm group was 19 mL and in the placebo group was 6 mL.

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Table 12: Study O99009 Double Blind Period (Part I) Average Urinary Volume per Void (mITT population)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Average urinary volume per void (mL)								
Baseline (Visit 3)								
Mean and SD	175.2	67.87	165.2	67.74	156.4	65.52	170.4	66.17
Median	168.0		163.0		147.0		168.0	
Endpoint change from baseline								
Mean and SD	12.8	59.05	8.8	67.64	25.1	58.01	31.8	67.56
Median	6.0		5.0		19.0		24.0	
P-value[1]			0.7379		0.0219		0.0063	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

* Table 14.2.1.1.3.1 in Vol. 46 on pg. 80-81; Listing 16.2.7.1.1; Appendix 16.1.9.2.1.3, p. 150

It is pertinent to compare Table 12 with the same data in Table 13 for the ITT population (labeled as the rITT in the Statistical Review) and in Table 14 for the mITT population excluding Site #12 for consistency with the two previously discussed key efficacy endpoints.

Table 13: Study O99009 Double Blind Period (Part I) Average Urinary Volume per Void (ITT population)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 131		n = 130		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Average urinary volume per void (mL)								
Baseline (Visit 3)								
Mean and SD	175.2	67.87	165.2	67.03	157.6	65.99	169.1	66.68
Median	168.0		163.5		149.0		164.0	
Endpoint change from baseline								
Mean and SD	12.8	59.05	8.6	68.43	25.1	56.83	32.1	67.53
Median	6.0		5.5		17.0		26.0	
P-value[1]			0.7032		0.0160		0.0085	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

* Table 14.2.1.0.3 in Vol. 46 on pg. 70-71

Table 14: Study O99009 Double Blind Period (Part I) Average Urinary Volume per Void (mITT population excluding Site #12)*

	Placebo		Oxybutynin TDS					
			13 cm^2		26 cm^2		39 cm^2	
	n = 130		n = 130		n = 131		n = 124	
	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD	Mean/ Median	SD
Average urinary volume per void (mL)								
Baseline (Visit 3)								
Mean and SD	175.3	68.71	164.5	68.23	155.9	64.53	171.6	65.10
Median	166.5		162.0		145.5		168.0	
Endpoint change from baseline								
Mean and SD	11.3	57.09	8.3	68.31	24.6	58.49	31.2	66.01
Median	6.0		4.5		18.0		26.0	
P-value[1]			0.7396		0.0255		0.0034	

[1]P-value derived from Dunnett's test; Comparison significant if $p < 0.05$; Active treatment vs. placebo

* Table 14.2.1.1.5.3 in Vol. 46 on pg.89-90

A **median** statistically significant treatment effect for the 39 cm^2 mITT treatment group compared to placebo was noted beginning at Visit 4 (Week 3) and was maintained throughout the double blind period (Table 14.2.1.1.3.1 in Vol. 46 on pg. 80-81). A **median** statistically significant treatment effect for the 26 cm^2 treatment group compared to placebo was noted beginning at Visit 6 (Week 9) and was continued through Visit 7 (Week 12) (Table 14.2.1.1.3.1 in Vol. 46 on pg. 80-81). If Site #12 is omitted from the mITT cohort, the statistical significance described above for the 26 cm^2 and 39 cm^2 treatment groups are maintained.

Medical Officer's Comments

- **While the actual treatment effects for volume voided were numerically small, these may indicate an increasing pharmacologic effect with increasing dose.**

8.2.5.3.3 Compare the mean Global Assessment of Disease State at baseline to Week 12

Patients experienced a decrease from baseline to end of treatment in the Global Assessment of Disease State score (Vol. 45 on pg. 79), however a comparison of results between placebo and drug groups did not reach statistical significance in the double-blind period. No further assessment was made.

8.2.5.3.4 Qualify of Life Instruments (IIQ, SF-36 and UDI) at baseline to Week 12

During the double-blind treatment period (Part I) regarding the Incontinence Impact Questionnaire (IIQ), only the 39 cm^2 treatment group demonstrated a statistical improvement ($p=0.0327$) in mean IIQ total score from baseline when compared to placebo. The mean IIQ total score for the mITT **39 cm^2** treatment group at baseline was 144.3 (SD 82.5) and at end of double blind period (LOCF) was 89.1 (SD 83.4), resulting in a mean change from baseline of -56.0 (SD 73.8) or a **39% improvement.** The mean IIQ total score for the mITT **placebo** treatment group at baseline was 159.3 (SD 94.3) and at end of double blind period (LOCF) was 113.3 (SD 93.8), resulting in a mean change from baseline of -44.3 (SD 70.9) or a **28% improvement.**

No significance treatment effects were observed for the Short Form 36 (SF-36) or Urogenital Distress Inventory (UDI) questionnaires (Vol. 45 on pg. 81). No further assessments of the SF-36 or UDI were made.

8.2.6 Conclusions Regarding Demonstrated Efficacy

No significant efficacy of the oxybutynin 13 or 26 cm^2 TDS was demonstrated in Study O99009.

Limited efficacy of oxybutynin 39 cm^2 TDS was demonstrated in Study O99009 for urinary incontinence episodes, however the reviewer considers the efficacy demonstrated to be inadequate for approval. After deleting Site #12, no statistically significant efficacy for urinary frequency was demonstrated by any treatment group.

8.2.7 Achievement of Protocol-Defined Primary Efficacy Endpoint

Approval was requested by the sponsor for the oxybutynin — 39 cm^2 TDS.

During the double-blind period, no mean or median efficacy was statistically demonstrated by the oxybutynin 13 or 26 cm^2 TDS treatment group for the primary efficacy endpoint, urinary incontinence episodes and the mean and median change from baseline in the oxybutynin 26 cm^2 TDS group were worse than placebo

During the double-blind period, mean efficacy was not statistically demonstrated in the oxybutynin 39 cm^2 TDS treatment group for the primary efficacy endpoint episodes of urinary incontinence. Only median efficacy was statistically demonstrated by the oxybutynin 39 cm^2 TDS treatment group for the primary efficacy endpoint (urinary incontinence episodes). When Site #12 was deleted from the analysis, no statistically significant efficacy for urinary frequency was demonstrated by any treatment group. The efficacy demonstrated by the oxybutynin 39 cm^2 TDS treatment group is not felt by this reviewer to be clinically significant. Nonapproval of the oxybutynin 39 cm^2 TDS based on inadequate efficacy is recommended.

8.2.8 Support of Label Efficacy Claim

Label review will be completed after oxybutynin TDS is found to be approvable.

8.3 Supportive Efficacy Study 096017

8.3.1 Overall Design

Study 096017 was a Phase II multicenter, randomized, double-blind, controlled, parallel-arm, dose-titration trial which consisted of three periods: a baseline evaluation when the patients were receiving their usual oral oxybutynin regimens, followed by a pretreatment (washout) period of 1-2 weeks, and then followed by a treatment period of 6 weeks. It was planned that a total of 70 patients would be enrolled in a maximum of eight centers. Patients were enrolled if they had a history of urge urinary incontinence associated with detrusor instability or detrusor hyperreflexia and if they had had symptomatic improvement on treatment with oral oxybutynin. Each eligible patient completed a urinary diary, an Anticholinergic Symptoms and Efficacy Questionnaire, and underwent a physical examination during the baseline evaluation followed by a washout period of 1-2 weeks from current oral oxybutynin therapy (pretreatment period). Those patients who demonstrated an increased number of incontinence episodes after discontinuation of oral oxybutynin in the pretreatment period underwent cystometry and were randomized in a 1:1 ratio to receive either — oxybutynin TDS or oral oxybutynin. The number of oxybutynin (or placebo) TDS worn at one time and the oral regimen of oxybutynin 2.5 mg capsules (or placebo) was initiated based on the patient's prior stable oral oxybutynin daily dose. The dose of oxybutynin was titrated at the completion of 2 and 4 weeks of treatment based on the patient reporting of adverse events. Each oxybutynin 13 cm^2 TDS contained 12 mg oxybutynin and was 13 cm^2 in surface area. The dose of oxybutynin delivered in each — oxybutynin TDS was 1.3 mg/day. The oxybutynin 13 cm^2 TDS dosing ranged from one to four TDS applied twice a week (i.e. transdermal oxybutynin dose ranged from 1-8 mg/day). Oral oxybutynin dosing ranged from one oxybutynin 2.5 mg capsule taken bid to three oxybutynin

capsules taken tid (i.e. oral oxybutynin dose ranged from 5 to 22.5 mg/day). Patients completed a urinary diary and the Anticholinergic Symptoms and Efficacy Questionnaire at the end of weeks 2, 4, and 6 and underwent a physical examination and cystometry at the end of treatment. Statistical analysis was conducted to evaluate equivalency in efficacy between transdermal and oral oxybutynin therapy based on the percentages of responders in each treatment group. Responders were patients who demonstrated a ≥30% decrease from baseline to endpoint in the number of daily incontinence episodes during treatment. Patients were eligible to be a responder if they completed at least 4 weeks of treatment

Medical Officer's Comments

- **The six-week treatment period in Study O96017 was significantly shorter than the 12-week treatment period for overactive bladder clinical trials intended to support efficacy.**
- **The dose titration design resulted in unequal numbers of patients ending the study on various doses. Of the 38 patients treated with oxybutynin TDS in Study O96017, the majority (n=26 or 68%) ended the trial on oxybutynin 52 cm^2 TDS, which we were not asked to review for approval.[32] Study O96017 provides us with Week 4-6 treatment data for 2 patients on oxybutynin 26 cm^2 TDS and 10 patients on oxybutynin 39cm^2.[35] An insufficient number of patients completed Study O96017 on the oxybutynin 26 and 39 cm^2 TDS to provide supporting evidence of efficacy for the oxybutynin — 39 cm^2**
- **Study O96017 would have benefited from including a placebo arm to confirm if it was reasonable to define a responder as a patient with a ≥30% decrease from baseline to endpoint in the number of daily urinary incontinence episodes. The placebo group might have demonstrated a similar rate of responders as the treated groups.**
- **This study was enriched by including only patients who had benefited from prior anticholinergic therapy.**

8.3.2 Patients

For Study 096017, patients who had a history of urge urinary incontinence associated with idiopathic detrusor instability or detrusor hyperreflexia were enrolled after providing informed consent if they met the following criteria:

Inclusion Criteria

1. Male or female, ≥ 18 years of age.
2. History of urge urinary incontinence associated with detrusor instability or detrusor hyperreflexia.
3. Improvement of urinary incontinence on treatment with oral oxybutynin.
4. Treatment with oral oxybutynin or at least 6 weeks prior to study entry. Patients should have been maintained on a stable regimen oral oxybutynin ≤20 mg/day for at least two weeks prior to baseline evaluations.
5. Patients must be willing to discontinue oxybutynin therapy for 1-2 weeks.

Exclusion Criteria

1. History of allergy to oxybutynin.
2. History of allergy to transdermal medications.
3. History of major or active skin disorders.

[35] NDA 21-351 Vol. 137 Listing 9.4-5, pg. 32-33.

4. Pregnancy or lactating women, or women of child-bearing potential who cannot use an adequate means of contraception during the study period.
5. Patients with significant stress incontinence.
6. Patients with overflow incontinence secondary to underactive or acontractile detrusor or outlet obstruction.
7. Patients with impaired bladder compliance (tonic rise in pressure above 15 cm H_2O during filling cystometry).
8. Patients who fail to demonstrate deterioration of urge urinary incontinence within 2 weeks after discontinuation of oxybutynin.
9. Treatment with any investigational drug within 30 days prior to initial dosing of transdermal oxybutynin or placebo.
10. Excessive consumption of caffeine (>10 cups of coffee, tea or cola daily).
11. Concurrent use of medication that may affect detrusor activity including: Anticholinergic agents: propantheline, dicyclomine, flavoxate, hyoscyamine. Tricyclic antidepressants: imipramine, doxepin, desipramine, nortriptyline.
12. Presence of reversible conditions that may cause urinary incontinence or urgency, such as urinary tract infections, atrophic vaginitis, urethritis, stool impaction, use of diuretics or antipsychotics, excessive use of alcohol.
13. History of glaucoma.
14. Clinically significant abnormalities in the screening EKG.
15. Abnormalities in the screening chemistries or hematologic laboratory values. Minor deviations, considered to be clinically insignificant by the investigator, may be allowed.
16. Concurrent use of medications that may affect the pharmacokinetics of oxybutynin, e.g. phenytoin, phenobarbital, cimetidine.
17. History of significant medical problems that may confound the outcome of this study.
18. Patients whose history shows exclusively urge symptoms without leakage of urine.
19. Presence of significant gastrointestinal disease that may affect the absorption of oral oxybutynin.
20. Patients who cannot maintain their usual level of fluid intake during this study.
21. Patients who cannot maintain unchanged their usual programs of nonpharmacologic management of incontinence (e.g. pelvic floor exercise, timed voiding/bladder training) during this study.
22. Patients who are judged unsuitable for enrollment for any reasons by the investigator.

8.3.3 Study Drugs

8.3.3.1 Dose Selection

The transdermal or oral oxybutynin (or placebo) regiments were initiated at one of three levels according to the patient/ prior stable daily oral oxybutynin dose and then maintained at that level from days 1 through 15 of the treatment phase as below:

Dose level	Prior stable oral oxybutynin daily dose at baseline evaluation	Transdermal oxybutynin/placebo regimen	Oral oxybutynin/placebo regimen
Level 1	≤10 mg	Two 13 cm^2 TDS twice a week (oxybutynin dose 2-4 mg/day)	2 capsules bid (oxybutynin dose 10 mg/day)
Level 2	11-15 mg	Three 13 cm^2 TDS twice a week (oxybutynin dose 3-6 mg/day)	2 capsules tid (oxybutynin dose 15 mg/day)
Level 3	16-20 mg	Four 13 cm^2 TDS twice a week (oxybutynin dose 4-8 mg/day)	3 capsules tid (oxybutynin dose 22.5 mg/day)

Each hard gelatin capsule contained oxybutynin 2.5 mg or placebo. Each TDS contained 12 mg oxybutynin, was 13 cm^2 in surface area, and was a matrix type system covered by an occlusive flexible polymer backing film or was a placebo system with the adhesive matrix without oxybutynin. The estimated systemic absorption from the transdermal oxybutynin system, based on prior in vitro and in vivo studies, was 1.3 mg/day of oxybutynin.

Between days 12 and 15, the patients completed a 3-day urinary diary and the Anticholinergic Symptoms and Efficacy Questionnaire to assess efficacy and specific side effects. On day 15, the transdermal and oral regimens were adjusted according to the severity of the patients' reported side effects and then maintained at that level from day 16-29 as below:

	Current dose level		
	Level 1	Level 2	Level 3
Intolerable side-effects	Decrease to one 13 cm^2 TDS twice a week (oxybutynin 1-2 mg/day) or 1 oral capsule bid (oxybutynin 5 mg/day)	Decrease to Level 1	Decrease to Level 2
Tolerable side effects	No change	No change	No change
No or mild side-effects	Increase to Level 2	Increase to Level 3	No change

Between day 26 and 29, the patients again completed a 3-day urinary diary and the Anticholinergic Symptoms and Efficacy Questionnaire to assess efficacy and specific side effects. On day 29, the transdermal and oral regimens were adjusted as listed above according to the severity of the patients' reported side effects and then maintained at that level from day 29-43.

8.3.3.2 Assignment to Study Drug

Patients were randomly assigned to transdermal oxybutynin or active control treatment according to a 1:1 randomization scheme. Patients were not stratified.

Medical Officer's Comments

- **Without additional supporting efficacy data, the reviewer cannot accept that the transdermal oxybutynin daily dose range of 1-8 mg/day is equivalent to the oral oxybutynin daily dose range of 5-22.5 mg/day.**

8.3.4 Study Procedures and Conduct

8.3.4.1 Schedule of Study Assessments

During the baseline evaluation after signing informed consent, the patient's eligibility for the study was determined according to the inclusion and exclusion criteria. A medical history, physical examination, 12-lead ECG, vital signs, and multichannel cystometry was performed, a 3-day urinary diary completed, urine sample collected for urinalysis and pregnancy (in female patients only), blood drawn for hematology, serum chemistries, and baseline oxybutynin and N-desethyloxybutynin plasma concentrations, and the Anticholinergic Symptoms and Efficacy Questionnaire completed by the patient.

During the pretreatment (washout period) of 1-2 weeks, patients were instructed to maintain their usual fluid intake and to maintain their usual programs of nonpharmacologic management of incontinence throughout the study. Between days 5 and 8 of this period, the patients completed a 3-day urinary diary and the Anticholinergic Symptoms and Efficacy Questionnaire. Patients who demonstrated worsening symptoms of incontinence (i.e. $\geq$3 episodes of urine leakage per day and an increase in the frequency of incontinence episodes by $\geq$30% compared to baseline evaluation) were entered into treatment period. For patients who did not fit the above criteria, oral oxybutynin was withheld for another week and the above procedures repeated.

During the treatment phase of 6 weeks, all patients underwent a cystometrogram prior to receiving any study medications. Patients were randomized in a 1:1 ratio in blocks of 8 and began treatment. Careful instruction in the correct technique of applying the TDS was given. The dose of oxybutynin could be titrated according to adverse events after 2 and 4 weeks of treatment. During visits after completing 2, 4, and 6 weeks of treatment, vital signs were measured, adverse event information was elicited, adhesion of current systems was assessed, concurrent medications were recorded, the Anticholinergic Symptoms and Efficacy Questionnaire was completed, and 3-day urinary diary information reviewed. Local tolerability and skin appearance was also assessed during clinical visits by visual inspection of the areas directly beneath previous system applications. Blood samples for measurement of plasma oxybutynin and N-desethyloxybutynin concentrations was collected on days 13-14, 27-28, and 41-42. At the end of the six-week treatment period, subjects underwent a physical examination, ECG, cystometrogram, and laboratory tests for serum chemistries, hematology and urinalysis.

Table 15. Study O96017 Original Schedule of Events*

Assessments	Baseline Evaluation	Pretreatment Period	Treatment Period (Weeks)					
			1	2	3	4	5	6
Informed Consent	X							
Physical Examination	X							X
Vital Signs	X	X		X		X		X
Urinalysis	X							X
ECG	X							X
Serum Chemistries	X							X
CBC	X							X
Urine beta-HCG[1]	X							
3-day Urinary Diary[2]	X	X		X		X		X
Cystometry		X						X
Anticholinergic Symptoms and Efficacy Questionnaire	X	X		X		X		X
Plasma Concentration	X			X		X		X
Skin Assessment				X		X		X
Adhesion Assessment				X		X		X

* Vol. 135 pg. 168

[1] Urine beta-HCG test were only performed on female patients of childbearing potential

Medical Officer's Comments

- **The reviewer believes that the protocol (in Vol. 135 on pg. 148) incorrectly lists cystometry as a baseline evaluation study procedure, since the Schedule of Events lists cystometry as a pretreatment study procedure.**

8.3.4.2 Key Efficacy Assessments

Primary efficacy endpoint was:

- Percentage of responders in each treatment group after 6 weeks of treatment. Patients will be categorized as responders or non-responders to treatment based on the difference in the number of incontinence episodes reported prior to and during treatment. Responders were patients who demonstrated a $\geq$30 % decrease from baseline to endpoint in the number of daily incontinence episodes during treatment. Patients who completed at least 4 weeks of treatment with oxybutynin were considered evaluable for efficacy.

Secondary efficacy endpoints were:

- Comparison of the subjective perception of the severity of urinary incontinence by visual analogue system scoring, urodynamic parameters (i.e. maximum cystometric capacity in mL and volume at first detrusor contraction in mL), and side-effect profile between oral and transdermal administration of oxybutynin.

Laboratory procedures for efficacy assessments.

The protocol stated that plasma samples would be assayed for concentrations of oxybutynin and N-desethyloxybutynin according to a validated analytical method. It also stated that the Analytical Laboratory would provide a report detailing method validation, measured concentrations, controls from each assay run, and references to the location of source documentation.

8.3.4.3 Pharmacokinetic Assessments

A "trough" blood sample was obtained during the baseline evaluation on all patients prior to the regular morning dose of oxybutynin. Three additional blood samples were collected during the treatment period. These samples were "trough" samples for the oral oxybutynin group and were "steady-state" samples for the transdermal oxybutynin group. Samples were drawn prior to the regularly scheduled morning dose of medication or after selected TDS application as follows:

4^{th} dose (day 12): at 24-48 hours postdose (days 13-14);

8^{th} dose (day 26): at 24-48 hours postdose (days 27-28);

12^{th} dose (day 40): at 24-48 hours postdose (days 41-42), same time as the last cystometry

8.3.5 Results

8.3.5.1 Demographics and Baseline Disease Characteristics

Twelve US sites each enrolled 1 to 12 patients for a total of 76 patients. A total of 91 patients were screened. Baseline demographic characteristics for the intent-to-treat and evaluable populations in Table 16. The majority of patients in each of the trials were Caucasian. Mean treatment group ages ranged from 63 to 64 years while individual ages ranged from 27 to 86 years. The first patient was enrolled on October 6, 1997 and the last patient completed the study on December 16, 1998.

Table 16. Study O96017 Demographics and Baseline Disease Characteristics*

	Intent to Treat		Evaluable	
	Oral N = 38	Transdermal N = 38	Oral N = 35	Transdermal N = 37
Race/Ethnicity				
Caucasian [n(%)]	36 (95%)	36 (95%)	34 (97%)	35 (95%)
African American [n(%)]	2 (5%)	2 (5%)	1 (3%)	2 (5%)
Gender				
Female [n(%)]	37 (97%)	33 (87%)	34 (97%)	32 (86%)
Male [n(%)]	1 (3%)	5 (13%)	1 (3%)	5 (14%)
Age (yr.)				
Mean (SD)	63 (14)	64 (15)	63 (13)	64 (15)
Incontinence Hx				
Urge	37	36	34	35
Mixed	1	2	1	2

*Derived from Table 5.2-1 in Vol.134 on pg. 41 and Tables 8-4B and 8-4C in Vol. 135 on pg. 9-10.

Medical Officer's Comments

- **Very few minority patients participated in Study O96017. The majority of patients in overactive bladder trials are Caucasian women.**

8.3.5.2 Primary Efficacy Analysis and Endpoint

When defining responders as patients who demonstrated a ≥30% decrease from baseline to endpoint in the number of daily incontinence episodes during treatment, in the **evaluable** patients (Table 8-7A in Vol. 135 on pg. 17), 86% of transdermal patients responded to treatment versus 89% in the oral group, yielding a 95% confidence interval of –17% to + 13% for the difference in % response of –2%. For the **ITT** patients (Table 8-7B in Vol. 135 on pg. 17), 84% of transdermal patients responded to treatment versus 89% in the oral group, yielding a 95% confidence interval of –20% to + 10% for the difference in % response of –5%. The confidence interval for the between treatment difference (both ITT and evaluable) was not completely contained in the interval –15% to 15% designated in the protocol for equivalence. The sponsor contended that this was because the study was underpowered, due to anticipating the high response rate of 95% in calculating the sample size. The response in the evaluable group to transdermal treatment increased between Weeks 2 through 6 from 68% to 86%, while the response remained relatively constant in the oral treatment group, increasing from 83% to 89%. Nine patients in the evaluable group did not respond to treatment, despite their history of prior response to oral oxybutynin (4 in oral group and 5 in transdermal group).

The average number (SD) of daily incontinence episodes in the **evaluable** patients (Table 8-8A in Vol. 135 on pg. 18) decreased from washout to Week 6: **mean** transdermal from 7.2 (4.5) to 2.4 (2.4); **mean** oral from 7.2 (4.0) to 2.6 (3.3). The average number (SD) of daily incontinence episodes in the **ITT** patients (Table 8-8B in Vol. 135 on pg. 19) decreased from washout to "last visit": **mean** transdermal from mean 7.2 (4.4) to 2.5 (2.5); **mean** oral from 6.9 (4.1) to 2.4 (3.2).

It is pertinent to evaluate the efficacy data for the subjects who were on the two doses under consideration for approval at Week 4-6: of the 38 transdermal subjects at Week 4-6, 10 subjects were on three oxybutynin 13 cm^2 TDS (i.e. 39 cm^2) applied twice a week and 2 subjects were on two oxybutynin 13 cm^2 TDS (i.e. 26 cm^2) applied twice a week. Of the two subjects on 26 cm^2 at Week 4-

6, the responder rate was 100%. Of the 10 subjects on 39 cm^2 at Week 4-6, the responder rate was 90%.

Table 17. Study O96017 Efficacy Data for Subjects on Oxybutynin 26 cm^2 or 39 cm^2 TDS at Week 4-6*

Patient Number; Dose at Week 4-6	Washout # incontinence episodes	Week 4-6 # of incontinence episodes	Responder
#2; 39 cm^2	5.7	1 at Week 6	Yes
#17; 39 cm^2	3.3	3.3 at Week 6	No
#19; 39 cm^2	6	0 at Week 6	Yes
#50; 39 cm^2	3.3	2 at Week 6	Yes
#53; 39 cm^2	11.7	3 at Week 6	Yes
#58; 39 cm^2	4.7	0 at Week 6	Yes
#60; 26 cm^2	6.7	0 at Week 6	Yes
#67; 39 cm^2 (Dropped)	10	1.3 at Week 4	Yes
#106; 39 cm^2	3.7	0 at Week 6	Yes
#110; 39 cm^2	5.3	1.7 at Week 6	Yes
#125; 39 cm^2	3	0.7 at Week 6	Yes
#134; 26 cm^2	5.7	1 at Week 6	Yes

*Data complied from Listing 9.4-3 in Vol.137 p. 21-28 and Listing 9.4-5 in Vol. 137 p. 32-33.

Medical Officer's Comments

- **The transdermal oxybutynin group required a longer treatment time before becoming "responders" when compared to the oral oxybutynin group. The increased treatment time was probably due to needing to titrate the dose up to Level 3 (i.e. four oxybutynin 13 cm^2 TDS or 52 cm^2) in the majority of patients in the transdermal oxybutynin group. Again, it is important to note that the sponsor does not seek approval of the 52 cm^2 dose.**

8.3.5.3 Secondary Efficacy Analysis and Endpoints

Patient rated (visual analog scale) control of urinary leakage was significantly reduced by both treatments when comparing washout to last visit ($p<0.0001$). There was no difference between treatments ($p=0.9$). Cystometry in both treatment groups demonstrated expected changes with oxybutynin treatment, increased volume to first detrusor contractions and increased maximum bladder capacity.

Table 18. Study O96017 Mean (SD) Bladder Volume (ml) at First Detrusor Contraction in Evaluable Patients*

	Oral	Transdermal
Number of Patients	30	33
Washout Volume (ml)	267 (187)	165 (158)
Last Visit Volume (ml)	302 (198)	229 (189)
Last Visit-Washout Difference (ml)	45 (163)	66 (126)

*From Table 5.9-1 in Vol. 134 on pg. 54.

Table 19. Study O96017 Mean (SD) Maximum Bladder Capacity (ml) in Evaluable Patients*

	Oral	Transdermal
Number of Patients	30	35
Washout Volume (ml)	342 (167)	244 (168)
Last Visit Volume (ml)	387 (162)	297 (176)
Last Visit-Washout Difference (ml)	51 (138)	53 (88)

*From Table 5.9-3 in Vol. 134 on pg. 55.

8.3.6 Conclusions Regarding Demonstrated Efficacy

Overall, the reviewer concluded that Study **O96017** demonstrated somewhat comparable treatment efficacy between oral oxybutynin Level 2 (i.e. oral oxybutynin 15 mg/day) and transdermal oxybutynin Level 3 (i.e. oxybutynin 52 cm^2 TDS twice weekly), however equivalence was not statistically demonstrated. This comparability is not relevant to the regulatory decision since the 52 cm^2 TDS is not up for approval.

8.3.7 Achievement of Protocol-Defined Primary Efficacy Endpoint

The study just failed on its primary efficacy endpoint, equivalence in the responder rate for the oral and transdermal oxybutynin groups, in both the evaluable and intent-to-treat analysis populations. Equivalence was not demonstrated between the oral and transdermal oxybutynin groups, despite the majority of patients (68%) in the transdermal treatment group reaching Level 3 dosing (i.e. oxybutynin 52 cm^2 TDS twice weekly), the maximum dose, by the end of 6 weeks of treatment while only 32% of patients in the oral treatment group reached Level 3 dosing (i.e. oral oxybutynin 22.5 mg/day) by the end of 6 weeks of treatment.

8.3.8 Support of Label Efficacy Claim

No labeling claims are supported by the Phase II study **O96017**.

8.4 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoint)

The validity of the sponsor's analyses of the primary efficacy endpoint was evaluated by the FDA statistician, Sue-Jane Wang, Ph.D.[36] Dr. Wang notes that an unplanned interim analysis was conducted during this study after approximately 50% of the patients had completed the study. When Dr. Wang performed an equivalence analysis based on both the evaluable patient and on the ITT patients, with and without a penalty for the unplanned interim analysis, the 95% confidence limit always fell outside –15% and +15% limits. She concluded that by the pre-specified statistical criteria, the study failed on the primary efficacy outcome, the responder rate: the responder rate in the TDS oxybutynin treated group was not equivalent to the oral oxybutynin treated group.

8.5 Medical Officer's Overall Assessment of Efficacy (Statistical and Clinical Significance)

The sponsor submitted only one Phase III trial, **O99009**, which failed to demonstrate efficacy for the oxybutynin 13 and 26 cm^2 TDS groups when compared to placebo. Efficacy was not demonstrated for the oxybutynin 39 cm^2 TDS group when the prespecified parametric ANCOVA analysis (i.e. means) was performed, however the normality assumption of the parametric ANCOVA was not met. Statistically significant efficacy was demonstrated in the oxybutynin 39 cm^2 TDS group for urinary incontinence episodes only by the non-parametric ranking procedure (i.e. medians). Statistically significant efficacy for the oxybutynin 39 cm^2 TDS group was not demonstrated by parametric (i.e. means) or nonparametric (i.e. medians) analysis for urinary frequency after Site #12 was deleted from the analysis. Since approximately 50% of overactive bladder patients demonstrate frequency without

[36] Wang S. NDA 21-351 Statistical Review and Evaluation, pg. 12-15.

urinary incontinence[37], and because evidence of efficacy for the 39 cm^2 TDS for frequency was not demonstrated, and because the sponsor has not provided substantial evidence to establish efficacy, nonapproval based on inadequate efficacy is recommended.

The small Phase II trial, **O96017**, was an underpowered study which failed on its primary efficacy endpoint, equivalence in the responder rate for the oral and transdermal oxybutynin groups, in both the evaluable and intent-to-treat analysis populations. Of clinical and regulatory significance is the fact that the majority of patients (68%) in the transdermal treatment group reached Level 3 dosing (i.e. oxybutynin 52 cm^2 TDS twice weekly), the maximum dose, by the end of 6 weeks of treatment while only 32% of patients in the oral treatment group reached Level 3 dosing (i.e. oral oxybutynin 22.5 mg/day) by the end of 6 weeks of treatment. The sponsor did not submit the 52 cm^2 TDS for registration.

9 INTEGRATED REVIEW OF SAFETY

9.1 Safety Studies

Data from 6 integrated US clinical studies and 10 nonintegrated studies (2 US dermatotoxicity studies and 8 Japanese pharmacokinetic and/or skin tolerability studies) were submitted by the Sponsor to support the safety of oxybutynin TDS. It should be noted that for Study O99009, only data from the double blind (Part 1) and open label safety (Part 2) periods were submitted in NDA 21-351. Data from Protocol O99009 safety extension (Part 3) period was reported in the 120-day Safety Update Report as a supplement to the Final Clinical Study Report. Section 6.2 of this review provided an overview of these clinical studies. The 6 integrated US clinical studies were the following:

- O96003 "Pharmacokinetics and Metabolism of Oxybutynin Following Application of the — Oxybutynin Transdermal System (OTS) and Administration of Oral Tablet in Healthy Volunteers"
- O99005 "Single-Dose Pharmacokinetics of Oxybutynin Following Oral and Transdermal Administration in Healthy Volunteers"
- O99006 "Single-Dose Pharmacokinetics of Oxybutynin following Transdermal Administration to the Abdomen, Buttocks, and Hip in Healthy Volunteers"
- O99007 "Steady-State Pharmacokinetics and Dose Proportionality of Oxybutynin Following Multiple Transdermal Applications in Healthy Volunteers
- O96017 "A Multi-Center Randomized, Double-Blind, Dose-Titration Study of the Effect of Oral (Ditropan®) versus Transdermal (— Oxybutynin in Patients with Urge Incontinence"
- O99009 "Transdermal Oxybutynin in Patients with Urge Urinary Incontinence: A 12-Week Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study with a 12-Week Open-Label, Dose-Titration Safety Period and a 28-Week Open-Label Safety Extension"

The 8 Japanese studies were excluded from the integrated safety report since only summaries were provided. The US dermatotoxicity studies (O96004 and O96005) were excluded from the integrated safety report since the subjects were exposed to significantly less oxybutynin (oxybutynin 5 cm^2 TDS containing approximately 6.5 mg oxybutynin) than in the integrated studies.

[37] Abrams P and Wein A. Introduction: Overactive Bladder and Its Treatments. *Urology*. 2000; 55 (5A): 1-2.

9.1.1 Exposure to Oxybutynin Transdermal System

At the time of NDA submission, a total of 855 subjects (542 patients and 313 healthy volunteers) had received at least one dose of oxybutynin TDS. In the integrated safety studies, a total of 542 overactive bladder patients and 83 healthy volunteers were exposed to any dose of oxybutynin TDS, of which:

- 24 healthy volunteers were exposed to oxybutynin 26 cm^2 TDS
- 436 overactive bladder patients were exposed to oxybutynin 26 cm^2 TDS
- 68 healthy volunteers were exposed to oxybutynin 39 cm^2 TDS
- 331 overactive bladder patients were exposed to oxybutynin 39 cm^2 TDS

It should be noted that any one patient could have been, and probably was, included in the exposure totals for more than one dose of oxybutynin TDS.

It should be noted that prolonged exposure to oxybutynin TDS only occurred during Protocol O99009. The 120-Safety Update Report Table 14.3.5.1.4.3 in Vol. 1 on pg. 462 states:

- 46 patients were exposed for at least 26 weeks (i.e. 6 months) to oxybutynin 26 cm^2 TDS
- 0 patients were exposed for at least 52 weeks (i.e. at least 1 year)) to oxybutynin 26 cm^2 TDS
- 64 patients were exposed for at least 26 weeks (i.e. 6 months) to oxybutynin 39 cm^2 TDS
- 1 patient was exposed for at least 52 weeks (i.e. 1 year) to oxybutynin 39 cm^2 TDS

There were no important differences in length of exposure within geriatric, gender, or race subpopulations and between each of these categories and the overall population (Vol. 30 on pg. 47).

Medical Officer's Comment.

- **Overall, this is a small safety database, however the extensive data previously submitted for oral oxybutynin must be taken into consideration.**
- **If exposure to any dose of oxybutynin TDS was considered, 66 patients have been exposed for at least one year[38], of which:**

  9 patients were exposed to oxybutynin 13 cm^2 for the majority of the year[27]

  22 patients were exposed to oxybutynin 26 cm^2 for the majority of the year[27]

  35 patients were exposed to oxybutynin 39 cm^2 for the majority of the year[39]
- **The sponsor argues in correspondence dated January 16, 2002 that since the primary risk from Oxytrol™ is associated with the transdermal system and the dermal exposure to oxybutynin, that all dose levels are appropriate for inclusion in defining the transdermal safety profile since the formulation is the same for all product strengths. The reviewer rejects this argument since the incidence of all application site adverse events increases with increasing dose of oxybutynin and severe treatment related adverse events occurred more frequently in the oxybutynin 39 cm^2 TDS group. The different oxybutynin transdermal dose groups do not have the same safety profile.**
- **The sponsor also argues in correspondence dated January 16, 2002 that since the duration of Study O99009-Part I and Part II was 24 weeks, then the exposure of patients to ≥24**

[38] NDA 21-351 Correspondence dated January 16, 2002.
[39] Listing 16.2.1.2.A in Attachment 2 NDA-231 Correspondence dated January 16, 2002.

weeks of oxybutynin is substantially greater than at ≥26 weeks (i.e. 6 months). The reviewer agrees with the sponsor's statement, however notes that this in only true if exposure to any dose of oxybutynin TDS was considered. Exposure to oxybutynin 13, 26, and 39 cm^2 TDS at least 24 weeks is essentially the same as at least 26 weeks (see Table 20).

Table 20. Extent of Patient Exposure to Oxybutynin by Dose

Interval	System Size			
	13 cm^2	26 cm^2	39 cm^2	Overall
At least 24 weeks	16	47	65	249
At least 26 weeks	15	46	64	149
At least 52 weeks	1	0	1	57

*Compiled from Table 14.3.5.1.4.3 in Vol. 1 of 120-day Safety Update Report pg. 461-463.

9.2 Protocol Defined Safety Assessments

Important safety assessments included treatment-emergent adverse events, skin tolerability, laboratory abnormalities, concomitant medication usage, physical examination findings, vital signs, electrocardiograms, system adherence assessment, and treatment compliance. Local tolerability to the TDS was assessed in all 6 integrated studies by visual inspection of the area directly beneath the TDS at different time intervals after the system was removed. Tolerability was rated in terms of the degree of erythema observed at the application site with a score of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe).

9.2.1 Adverse Events

Adverse events (AEs) were recorded and monitored throughout the clinical trials. Adverse events were elicited in O99009 by asking all patients at every visit if they have experienced any medically related changes in their well-being, had been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens. The nature, frequency, onset and resolution date and time, outcome, and treatment of AEs were recorded on the subject's case report form (CRF). In addition, in Study O96017, specific anticholinergic symptoms associated with oxybutynin treatment were documented in a questionnaire completed at baseline, during the pretreatment period, and at the end of Weeks 2, 4, and 6 of the treatment period. If the symptoms from the questionnaires fit the definition of an AE (i.e. symptoms not present at washout, symptom increased in severity, or symptom resolved and recurred at a later time point) they were entered as an adverse event, coded as related to study drug, and presented together with the other AEs.

9.2.2 Clinical Laboratory Tests

Hematology, serum chemistry, and urinalysis were performed at baseline and at study exit in Studies O99009 (Phase III), O96017 (Phase II), and O96003 (Phase I). In addition, blood samples were collected prior to dosing and at periodic intervals throughout study periods in all 6 integrated studied for evaluation of plasma concentrations of oxybutynin and its major active metabolite, N-desethyloxybutynin. No clinical laboratory test results were summarized for healthy volunteer subjects because laboratory assessments were performed only at baseline in 3 (O99005, O99006, and O99007) of the 4 healthy volunteer studies in the integrated safety report.

9.3 Patient Disposition

Of the 542 patients in the integrated safety studies who received at least one dose of oxybutynin TDS, 424 patients completed 12 weeks (Study O99009-Part I) and 258 patients completed 24 weeks (Study

O99009-Part I and Part II) of any dose of oxybutynin TDS treatment. Of the 542 patients in the integrated safety studies who received at least one dose of oxybutynin TDS, 117 (21.6%)[40] withdrew early, primarily because of adverse events (14.8%)[41]. Patient decision, noncompliance, protocol violations, and lost to follow-up accounted individually for <1.5% of early discontinuations in the double-blind (Part 1) and open label (Part 2) period of Study O99009[42]. Of the 83 healthy volunteers in the integrated safety studies, 4 discontinued early.

Medical Officer's Comment

- **The percentage of patients from the oxybutynin TDS group who prematurely withdrew due to adverse events was high (14.8%) and discontinuation rates tended to increase with increasing duration of exposure.**

9.4 Demographics and Other Baseline Characteristics (Integrated Safety Studies)

The sponsor did not pool the demographic and other baseline characteristics for the patients in the 6 integrated safety studies. Instead, they presented the demographic and baseline characteristics for four different populations from the 6 integrated safety studies as follows: 1) Healthy Volunteers, 2) Controlled Studies in U-UI Patients (Treatment ≤ 6 weeks), 3) Controlled Studies in U-UI Patients (0-12 weeks) and 4) Controlled and Uncontrolled Studies in Active TDS U-UI Patients.[43] The data in the tables for the four different populations were also presented according to the total daily dose and formulation. The oxybutynin TDS patient treatment groups in general were similar with respect to age (median 63 to 65 yr.), race (91-100% Caucasian), weight (161.1-179.6 lbs.), and sex (84.6-92.7% female) per Table 4.4 in Vol. 31 on pg. 99-100. The demographic subject data on TDS placebo patients in the controlled studies regarding age (median 64.5 yr.), race (89.4% Caucasian), weight (183.3 lbs.), and sex (91.7% female) can be located in Table 4.3 in Vol. 31 on pg. 89-92.

Medical Officer's Comment

- **Overall, the 4 active TDS treatment and placebo TDS groups for the U-UI patients appeared to be reasonably well balanced.**

9.5 Adverse Events

Adverse events for the **integrated safety studies** are presented and discussed in Sections 9.5.1 through 9.5.6 in the following manner:

- **Section 9.5.1** Overview of reported adverse events, based on the numbers of patients reporting adverse events summarized into broad categories
- **Section 9.5.2** Most commonly reported adverse events (all degrees of severity and all relationships to Study Drugs,)
- **Section 9.5.3** Most commonly reported adverse events possibly related to treatment with Study Drugs
- **Section 9.5.4** Treatment-related adverse events that resulted in withdrawal of patients from the clinical trials
- **Section 9.5.5** Severe treatment-related adverse events
- **Section 9.5.6** Nonfatal, serious treatment-related adverse events

[40] NDA 21-351 Vol. 30 pg. 38
[41] NDA 21-351 Vol. 30 pg. 55
[42] NDA 21-351 Vol. 30 pg. 38
[43] NDA 21-351 Table 6.2-1 in Vol. 30 on pg. 45-46

Adverse events for the nonintegrated studies are discussed in **Section 9.5.7**. Adverse events for Study O99009 safety extension (Part 3) of Study O99009 in **Section 9.5.8**.

9.5.1 Overview of Adverse Events (Integrated Safety Studies)

The overall incidence of treatment-emergent AEs was somewhat greater in U-UI patients on the active TDS (73.1%)[44] compared to the placebo TDS (62.1%)[45] groups. Drug-related AEs were also more common in U-UI patients on the active TDS (46.3%)[46] than TDS placebo-treated patients (32.6%)[47], with a trend toward higher incidence of AEs with increasing dose (21.9% with 13 cm^2, 23.4% with 26 cm^2, and 28.1% with 39 cm^2). The most common drug-related adverse events were application site reactions (22.7% of active TDS patients and in 9.1% of placebo TDS patients)[48] and dry mouth (occurring in 9.4% of active TDS patients per compared to 8.3% of placebo TDS patients)[49] in controlled trials.

Overall, 14.9% of patients discontinued active TDS treatment [50] due to treatment-emergent adverse events as compared to 4.5% of placebo TDS patients[51]. Overall, 3.1% of active TDS patients reported a treatment-emergent Serious Adverse Event[52] as compared to 3.8% of placebo TDS patients[53].

There were no deaths reported in healthy volunteers or in U-UI patients during treatment. Two patients died from non-study related causes, heart attack and malignant mixed Mullerian tumor: one prior to treatment initiation and one following study participation, respectively.

Table 21. Number of Active and Placebo TDS Patients Reporting Adverse Events in Integrated Safety Studies*

	Active TDS N = 542 n (%)	Placebo TDS N = 132 n (%)
All adverse events	396 (73.1)	82 (62.1)
Nonfatal serious	22 (3.1)	5 (3.8)
Treatment-related adverse events	251 (46.3)	43 (32.6)
Application site	120 (22.1)	12 (9.1)
Dry mouth	51 (9.4)	11 (8.3)
Withdrawals due to adverse events	81 (14.9)	6 (4.5)
Deaths during study	0 (0)	0 (0)

*Compiled from Table 6.3.2 in Vol. 32 on pg. 57-58 and 97, Table 6.7.2 in Vol. 37 on pg. 129-130 and 203, Table 7.3.1in Vol. 38 on pg. 119, Table 7.3.2 in Vol. 38 on pg. 138, Table 7.4.1 in Vol. 38 on pg. 180, and Table 7.4.2 in Vol. 38 on pg. 217

[44] **Table 6.7.2 in Vol. 37 on pg. 129**
[45] **Table 6.3.2 in Vol. 32 on pg. 57**
[46] **Table 6.7.2 in Vol. 37 on pg. 129**
[47] **Table 6.3.2 in Vol. 32 on pg. 57**
[48] **Table 6.7.2 in Vol. 37 on pg. 203**
[49] **Table 6.3.2 in Vol. 32 on pg. 97**
[50] **Table 7.4.1 in Vol. 38 on pg. 180**
[51] Table 7.3.1 in Vol. 38 on pg. 119
[52] Table 7.4.2 in Vol. 38 on pg. 217
[53] Table 7.3.2 in Vol. 38 on pg. 138

Table 22. **Number of Healthy Volunteers Reporting Adverse Events in Integrated Safety Studies**

	Active TDS N = 83 n (%)	5 mg Oral N = 33 n (%)
All adverse events	47 (56.6)	7 (21.2)
Nonfatal serious	0 (0)	0 (0)
Treatment-related adverse events	36 (43.4)	5 (15.2)
Application site	20 (24.1)	0 (0)
Dry mouth	4 (4.8)	0 (0)
Withdrawals due to adverse events	1 (1.2)	1 (3)
Deaths during study	0 (0)	0 (0)

*Compiled from Table 6.1.1in Vol. 31 on pg. 151 and Table 6.1.2 in Vol. 31 on pg. 154-155 and 181

Medical Officer's Comment

- **In Table 22, since only a single dose of 5 mg oral oxybutynin was administered, it is not appropriate to compare the incidence of adverse events reported by healthy volunteers who applied the active TDS for up to 96 hours with those who took a single dose of oral oxybutynin.**

9.5.2 Adverse Events (Integrated Safety Studies)

The most commonly reported treatment-emergent adverse events (all degrees of severity and all relationships to Study Drugs) for patients in the integrated safety studies is presented in Table 23 and for healthy volunteers in the integrated safety studies in Table 24. Application site AEs (including application site pruritus, erythema, hyperpigmentation, papules, burning, macules, oedema, petechiae, rash, reaction, vesicle, or pain) were the most common AEs and occurred in 22.1% of patients treated with active TDS. Pruritus was the most common application site AE at all dose levels and occurred at approximately 14% of patients receiving active treatment. The greatest incidence of application site reactions occurred within the first 12 weeks of treatment, followed by a decline with continued treatment. One patient exhibited contact sensitization. There were no significant differences in the incidence and frequency of AEs among the elderly patients when compared with patients < 65 years of age.

Medical Officer's Comment

- **It is notable that one patient exhibited contact sensitization in this trial despite negative results in the "contact sensitization" study (Protocol O96005).**

Table 23. Treatment-Emergent Adverse Events (All Treatment Relationships) Occurring in 5% or More of Active and Placebo TDS Patients by Preferred Term in the Integrated Safety Studies*

	Treatment Group					
Preferred Term	Placebo N=132 n (%)	13 cm^2 N=443 n (%)	26 cm^2 N = 436 n (%)	39 cm^2 N = 331 n (%)	52 cm^2 N=26 n (%)	Overall ActiveTDS N = 542 n (%)
Any Adverse Event	82 (62)	187 (42)	178(41)	156 (47)	12 (46)	396 (73)
Application Site Pruritus	8 (6)	17 (4)	33 (8)	28 (9)	0 (0)	76 (14)
Mouth Dry	11 (8)	13 (3)	19 (4)	18 (5)	1 (4)	51 (9)
Urinary Tract Infection	7 (5)	21 (5)	11 (3)	12 (4)	2 (8)	46 (9)
Diarrhea	10 (8)	10 (2)	19 (4)	10 (3)	0 (0)	38 (7)
Inflicted Injury	4 (3)	9 (2)	16 (4)	10 (3)	0 (0)	35 (7)
Headache	6 (5)	13 (3)	7 (2)	10 (3)	0 (0)	29 (5)
Application Site Erythema	3 (2)	8 (2)	8 (2)	12 (4)	0 (0)	26 (5)
Constipation	5 (4)	12 (3)	6 (1)	7 (2)	0 (0)	25 (5)
Nausea	7 (5)	9 (2)	8 (2)	4 (1)	1 (4)	22 (4)
Dysuria	0 (0)	1 (<1)	5 (1)	5 (2)	2 (8)	13 (2)
Somnolence	1 (1)	2 (1)	0 (0)	4 (1)	2 (8)	8 (2)
Urinary Retention	0 (0)	0 (0)	0 (0)	0 (0)	2 (8)	2 (<1)

*Compiled from Table 6.3.1 in Vol. 32 on pg. 51-52, Table 6.3.3 in Vol. 32 on pg. 359-383, Table 6.7.1 in Vol. 36 pg. 93-104, Table 6.7.3 in Vol. 38 pg. 31-85

Table 24. Treatment-Emergent Adverse Events (All Treatment Relationships) Occurring in 5% or More of Healthy Volunteers by Preferred Term in the Integrated Safety Studies*

	Treatment Group				
Preferred Term	Oxybutynin 5 mg oral N=33 n (%)	13 cm^2 N=41 n (%)	26 cm^2 N = 24 n (%)	39 cm^2 N = 68 n (%)	Overall TDS N = 83 n (%)
Any Adverse Event	7 (21)	14 (34)	13 (54)	34 (50)	47 (57)
Headache	2 (6)	5 (12)	3 (12)	13 (19)	18 (22)
Application Site Erythema	0 (0)	4 (10)	6 (25)	4 (6)	12 (15)
Nausea	2 (6)	2 (5)	2 (8)	4 (6)	8 (10)
Application Site Pruritus	0 (0)	3 (7)	0 (0)	4 (6)	5 (6)
Irritable Bowel Syndrome	0 (0)	0 (0)	0 (0)	5 (7)	5 (6)
Pharyngitis	0 (0)	1 (2)	2 (8)	4(6)	7 (8)
Abdominal Pain	0 (0)	1 (2)	1 (4)	3 (4)	5 (6)
Dizziness	2 (6)	0 (0)	1 (4)	3 (4)	4 (5)
Coughing	0 (0)	1 (2)	1 (4)	3 (4)	5 (6)
Application Site Hyperpigmentation	0 (0)	2 (5)	1 (4)	2 (3)	5 (6)
Mouth Dry	0 (0)	1 (2)	0 (0)	3 (4)	4 (5)
Application Site Rash	0 (0)	3 (7)	0 (0)	1 (1)	4 (5)
Rash	0 (0)	2 (5)	0 (0)	0 (0)	2 (2)

*Compiled from Table 8.1-1 in Vol. 30 on pg. 59 and Table 6.1.3 in Vol. 31 on pg. 216-227

Medical Officer's Comment

- **In Table 23, if the 52 cm^2 treatment group was deleted due to the small numbers of patients in that treatment group, then the % for dysuria, somnolence, and urinary retention would be less than 5% for the remaining treatment groups.**

9.5.3 Treatment-Related Adverse Events (Integrated Safety Studies)

The most common treatment-related adverse events from the integrated safety studies are presented in Tables 25 and 26.

Table 25. Treatment-Related Adverse Events (All Treatment Relationships) Occurring in 5% or More of Active and Placebo TDS Patients by Preferred Term in the Integrated Safety Studies*

	Treatment Group					
Preferred Term	Placebo N=132 n (%)	13 cm^2 N=443 n (%)	26 cm^2 N = 436 n (%)	39 cm^2 N = 331 n (%)	52 cm^2 N=26 n (%)	Overall ActiveTDS N = 542 n (%)
Drug-related Adverse Event	43 (33)	97 (22)	102 (23)	93 (28)	6 (23)	251 (46)
Application Site Pruritus	8 (6)	16 (4)	33 (8)	28 (9)	0 (0)	75 (14)
Mouth Dry	11 (8)	13 (3)	19 (4)	18 (5)	1 (4)	51 (9)
Headache	5 (4)					
Application Site Erythema	3 (2)	8 (2)	8 (2)	12 (4)	0 (0)	26 (5)
Dysuria	0 (0)	0 (0)	0 (0)	4 (1)	2 (8)	6 (1)
Somnolence	1 (1)	0 (0)	0 (0)	0 (0)	2 (8)	2 (<1)

*Compiled from Table 6.3.1 in Vol. 32 on pg. 51-52, Table 6.3.3 in Vol. 32 on pg. 359-383, Table 6.7.1 in Vol. 36 pg. 93-104, Table 6.7.3 in Vol. 38 pg. 31-85

Table 26. Treatment-Related Adverse Events (All Treatment Relationships) Occurring in 5% or More of Healthy Volunteers by Preferred Term in the Integrated Safety Studies*

	Treatment Group				
Preferred Term	Oxybutynin 5 mg oral N=33 n (%)	13 cm^2 N=41 n (%)	26 cm^2 N = 24 n (%)	39 cm^2 N = 68 n (%)	Overall TDS N = 83 n (%)
Drug-related Adverse Event	5 (15)	12 (29)	11 (46)	25 (37)	36 (43)
Headache	1 (3)	5 (12)	3 (12)	10 (15)	16 (19)
Application Site Erythema	0 (0)	4 (10)	6 (25)	4 (6)	12 (15)
Nausea	2 (6)	1 (2)	2 (8)	4 (6)	7 (8)
Application Site Pruritus	0 (0)	3 (7)	0 (0)	4 (6)	5 (6)
Dizziness	2 (6)	0 (0)	1 (4)	3 (4)	4 (5)
Application Site Hyperpigmentation	0 (0)	2 (5)	1 (4)	2 (3)	5 (6)
Mouth Dry	0 (0)	1 (2)	0 (0)	3 (4)	4 (5)
Application Site Rash	0 (0)	3 (7)	0 (0)	1 (1)	4 (5)
Rash	0 (0)	2 (5)	0 (0)	0 (0)	2 (2)

*Compiled from Table 8.1-1 in Vol. 30 on pg. 59 and Table 6.1.3 in Vol. 31 on pg. 216-227

Medical Officer's Comments

- **There are fewer preferred term listings (as expected) in the treatment-related adverse events Tables 25 and 26 than in the treatment-emergent adverse events Tables 23 and 24. Otherwise the treatment-related and treatment-emergent adverse event tables are similar.**
- **In Table 25, if the 52 cm^2 treatment group was deleted, due to the small numbers of patients in that treatment group, then the % for dysuria and somnolence would be less than 5% for the remaining treatment groups.**

9.5.4 Adverse Events Resulting in Patient Withdrawal (Integrated Safety Studies)

Overall, 14.9% (n=81) of integrated safety studies active TDS patients (n=542) discontinued treatment due to adverse events and 12.4% (n=67) of active TDS patients discontinued due to treatment-related AEs. Patient discontinuations due to adverse events were significantly more common in patient receiving active treatment compared to those receiving placebo (38 or 9% of active TDS patients versus 4 or 3% of placebo TDS patients if received $\leq$ 6 weeks of treatment; 51 or 12% of active TDS patients versus 6 or 4.5% of placebo TDS patients, if received 0-12 weeks of treatment). Discontinuation rates tended to increase with increasing duration of exposure.

The primary reason for discontinuations due to AEs was application site adverse events (43 out of 542 active TDS patients in the integrated studies or 7.9%). In the active TDS group, discontinuation due to application site AEs increased slightly with dose from 2.7% in the 13 cm^2 group to 4.8% in the 39 cm^2 group. In the TDS placebo group, only 1 patient discontinued due to an application site AE. Among anticholinergic AEs, dry mouth was the leading cause of discontinuations due to AEs, however few patients discontinued due to dry mouth (n=5 or 0.9% of active TDS group and none in TDS placebo group). Dizziness resulted in 4 patients in the active TDS group and no patients in the TDS placebo group prematurely discontinuing.

During the double-blind period of Study **O99009** (Part I), a total of 41 of 520 (7.9%) patients were withdrawn because of a treatment-related adverse event with the treatment groups as follows:

- 2 of 132 (1.5%) patients in the placebo group
- 13 of 130 (10%) patients in the oxybutynin 13 cm^2 TDS group
- 12 of 133 (9%) patients in the oxybutynin 26 cm^2 TDS group
- 14 of 125 (11.2 %) patients in the oxybutynin 39 cm^2 TDS group

Two subjects in the healthy volunteer integrated safety studies discontinued treatment due to AEs[54]:

- Subject 20004 in O99005 due to treatment-related headache (oxybutynin 39 cm^2 TDS group)
- Subject 10006 in O96003 due to treatment-nonrelated bronchitis (oral oxybutynin group)

Medical Officer's Comments

- **The listing of patients (Listing 7.5.2.1 in Vol. 38 on pg. 231-335) and healthy volunteers (Listing 7.5.1.1 in Vol. 38 on pg. 228-9) with adverse events leading to withdrawal was reviewed. It appears that transdermal oxybutynin may result in fewer discontinuations due to dry mouth than reported in oral oxybutynin studies, however the discontinuations due to application site AEs resulted in more discontinued patients overall.**

9.5.5 Severe Treatment-Related Adverse Events (Integrated Safety Studies)

A total of 1344 adverse events occurred in patients receiving active TDS treatment, of which 619 were considered to be treatment-related and 75 were considered to be severe treatment-related AEs

[54] NDA 21-351 Listing 7.5.1.1 in Vol. 38 on pg. 228-229

(Table 6.7.1 in Vol. 36 on pg. 102-3). In the integrated studies, most severe treatment-related adverse events (46 events or 61.3% of all severe AEs) were application site AEs and they occurred more frequently (17 events) in the 39 cm^2 TDS group. The total number of patients who reported a severe treatment related application site AE was 32 (Table 6.7.2 in Vol. 37 on pg. 128). Given that 542 patients were exposed to any active TDS application dose or number, this represents an incidence rate of severe application site treatment-related active TDS AE of 5.9 %. These severe application site AEs were reviewed individually in Table 6.7.2 in Vol. 37 on pg. 128-139 and were found to consist of:

14 patients with 18 severe treatment related AEs of application site erythema

8 patients with 10 severe treatment related AEs of application site pruritus

7 patients with 7 severe treatment related AEs of application site reaction

4 patients with 5 severe treatment related AEs of application site rash

3 patients with 5 severe treatment related AEs of application site vesicle

1 patient with 1 severe treatment related AE of application site petechiae

Only one patient in the active TDS group reported severe dry mouth compared to 8 patients in the overall oral oxybutynin group.

A total of 163 adverse events occurred in healthy volunteers receiving active TDS treatment, of which 106 were considered to be treatment-related and 3 were considered to be a severe treatment-related AEs: 2 vomiting, 1 nausea, and no application site severe treatment-related AEs (Table 6.1.1 in Vol.31 on pg. 151).

Medical Officer's Comments

- **24 of the 25 patients who dropped out of the Study O99009 double-blind period due to significant intolerability to the systems were receiving active TDS.**
- **The severe treatment-related adverse events appeared to reflect a pattern similar to the all treatment-related AEs.**

For additional safety information on skin tolerability, see Section 9.8.1 of this review.

9.5.6 Nonfatal, Serious Treatment-Related Adverse Events (Integrated Safety Studies)

In the integrated safety studies, 23 subjects reported a total of 29 serious adverse events (SAEs). No SAEs occurred in the healthy volunteer studies. None of the SAEs were considered to be related to the study drug. Seventeen of the 23 subjects with SAEs completed study. Most (26 of 29) of the SAEs resolved prior to study completion.

Medical Officer's Comments

- **Table 8.8-1 in Vol. 30 on pg. 90 entitled "Summary of treatment-emergent serious adverse events in integrated studies" was reviewed. It appeared reasonable that none of the SAEs were related to study drug.**

9.5.7 Adverse Events in Nonintegrated Studies

Of the 230 healthy volunteers in the 10 nonintegrated studies, 74 subjects reported a total of 155 adverse events. Approximately 1/3 of the subjects who reported adverse events (28 of 74 subjects) reported application site events. 27 subjects reported mild intensity application site events, one subject reported a moderate application site event. No severe application site AEs were reported. Less than 10% of the subjects who reported adverse events (5 of 74 subjects) reported anticholinergic symptoms related to oxybutynin such as dysuria, urinary retention, and blurred vision. Two subjects

reported a total of two serious events (which were considered to be not related to study drug) of back or elbow fractures. No deaths occurred in the nonintegrated studies.

Medical Officer's Comments

- **Appendix A in Vol. 30 on pg. 124-146 entitled "Safety summary from the nonintegrated studies in the clinical development program" was reviewed. It was noted that in 4 of the 10 nonintegrated studies (i.e. in 176 of the 230 healthy volunteers) a lower dose of oxybutynin TDS (i.e. oxybutynin 5 or 10 cm^2 TDS) was used than in the integrated U-UI patient studies (i.e. oxybutynin 13, 26, 39, and 52 cm^2 TDS). Therefore the lower incidence and lessened severity of application site AEs reported in the nonintegrated studies may be due to exposure to lower dose oxybutynin TDS.**

9.5.8 Adverse Events in the Safety Extension (Part III) of Study O99009

The results of the 28-week safety extension (Part III) of Study O99009 were submitted in the 120-day Safety Update Report on August 10, 2001 and included data on all patients who were treated through April 30, 2001. The last patient completed Part III of Study O99009 on April 19, 2001. Of the 142 patients enrolled in Study O99009-Part III at the ten sites (13 on 13 cm^2, 54 on 26 cm^2, and 75 on 39 cm^2), 115 (81%) completed the 28-week period (12 on 13 cm^2, 43 on 26 cm^2, and 60 on 39 cm^2). Ten patients (7%) withdrew due to adverse events, 2 because of protocol violations, 13 due to patient decision, and two were lost to follow-up. Of the 6 patients who discontinued due to drug-related AEs, all had AEs that involved application site reactions.

Safety evaluations included incidence and severity of AEs, physical examination, clinical laboratories and urine beta-human chorionic gonadotropin (for females of childbearing potential), electrocardiogram, and skin tolerability assessment.

A total of 250 adverse events were reported by 99 patients (70% of all patients) in Part III. A total of 33 adverse events reported in 23 patients were considered drug-related AEs. Five patients (3.5%) reported a severe, drug-related AE. The most frequently reported treatment-related AE was application site erythema, occurring in 5 patients (2.8%). Overall application site AEs were reported in 6.3% of patients (12 events in 9 patients). One patient on 39 cm^2 reported dry mouth, which was considered mild and treatment related. No deaths occurred; 7 patients reported a total of 8 Serious Adverse Events (SAE), none of which were felt to be related to study drug. Subject #0318 was a 41 year old female on 26 cm^2 who began Part III on August 15, 2000. She reported an exacerbation of multiple sclerosis began on [redacted]. She experienced bradycardia as a SAE on [redacted]. She was hospitalized, treatment was interrupted, the bradycardia resolved after 3 days, and the patient continued in the study. No hospital records were included with her case report form. She completed Part III with no further cardiac AEs.

Medical Officer's Comments

The 120-day Safety Update Report was reviewed. It was noted that a significantly lower percentage of patients in Study O99009 Part III reported application site reactions (6.3%) than in the integrated safety studies (22.1%), in Study O99009 Part I (18.3%), or in Study O990009 Part II (10.7%). This decreased percentage of patients with application site reactions in Study O99009 Part III may be due to patients with application site reactions during Study O99009 Part I or Part II withdrawing from the study. No significant and unexpected adverse events were noted.

9.6 Deaths or Pregnancy

No deaths were reported during treatment in any study. Two patients died from non-study-related causes, heart attack or malignant mixed Mullerian tumor, one prior to treatment and the other following study participation. One death occurred during the screening phase of Study O96017: an 86-year old female died of an apparent heart attack approximately 3.5 months after the initial

screening evaluation during the washout period from oral oxybutynin. One death occurred after discharge from the uncontrolled open-label period of Study O99009: a 73-year old female died after participation in the study of a malignant mixed Mullerian tumor of the endometrium.

One 30-year old patient (#2125) was discontinued from the double-blind period of Study O99009 due to pregnancy. She enrolled on February 8, 2000. During the double-blind period she was treated with 26 cm^2 TDS. She was discontinued from the study on June 12, 2000, upon notification of her pregnancy. On —— she miscarried at home. She did not receive any further medical care until —— when she had follow-up with her personal physician. It was felt that her miscarriage was not related to her participation in the study.

9.7 Laboratory Assessments

Laboratory data for the integrated safety studies were reviewed by the following process:

- Mean values, median values, and minimum and maximum for hematology tests with results expressed as percentage of Lower and Upper Normal Limit (calculated for each patient) at protocol-designated assessment times were reviewed for differences across treatment groups[55]

Medical Officer's Comment

No significant findings were noted.

- Mean values, median values, and minimum and maximum for serum chemistry tests with results expressed as percentage of Lower and Upper Normal Limit (calculated for each patient) at protocol-designated assessment times were reviewed for differences across treatment groups[56].

Medical Officer's Comment

Noted were 8 patients (at endpoint: 3 on placebo, 1 on oxybutynin 13 cm^2 and 4 at oxybutynin 26 cm^2) with elevated ALT (SGPT), 10 patients (at endpoint: 2 on placebo, 1 on oxybutynin 13 cm^2, 3 on oxybutynin 26 cm^2, and 4 on oxybutynin 39 cm^2) with elevated AST (SGOT), and 57 patients (at endpoint: 12 on placebo, 10 on oxybutynin 13 cm^2, 15 on oxybutynin 26 cm^2, 18 on oxybutynin 39 cm^2 and 2 on oxybutynin 52 cm^2) with elevated GGT. These elevations were not felt to occur at significantly different rates when comparing the four subject groups.

- Mean values, median values, and minimum and maximum for urinalysis pH and specific gravity with results expressed as percentage of Lower and Upper Normal Limit (calculated for each patient) and summary of abnormal (categorical analytes) urinalysis results at endpoint at protocol-designated assessment times were reviewed for differences across treatment groups Table 9.3.3.1 Part 3/3 in Vol. 39 on pg. 234, Table 9.3.3.2 Part 3/3 in Vol. 39 on pg.237, Table 9.3.3.3 Part 3/3 in Vol. 39 on pg. 246-249. No significant findings were noted except that in the 122 samples evaluated for bacteria, 100% were abnormal and contained bacteria.

Medical Officer's Comment

This result (100%) may be a mistake since over 400 urinalysis samples in Study O99009 were obtained.

- Notable laboratory values (abnormal values that were considered to be of particular concern based on the Sponsor's criteria) were reviewed.

For Study O99009 Part I and Part II, percentages of patients with laboratory values that shifted to outside of the normal range on one more or more occasions during treatment were reviewed for

[55] NDA 21-351 Vol. 39 Table 9.3.1.1 Part 3/3 on pg. 193-195 and Table 9.3.1.2 Part 3/3 on pg.201-203.
[56] NDA 21-351 Vol. 38 Table 9.1.2.1Part 1/2 on pg. 366 and Vol. 39 Table 9.3.2.1 Part 3/3 on pg. 216-221and Table 9.3.2.2 Part 3/3 on pg.228-234

differences across treatment groups.[57] For Study O99009 Part III, laboratory assessments were reviewed.[58]

Medical Officer's Comment

No significant findings were noted.

9.8 Safety Issues of Special Concern

9.8.1 Skin Tolerability

Skin tolerability data from studies where patients wore the actual oxybutynin 39 cm^2 TDS will be discussed first.

Study O99005

This was a randomized, open-label, two-period, crossover study. Subjects were randomized to sequence. The treatments administered were either one single dose of 5 mg oral oxybutynin and one single dose of oxybutynin TDS (39 cm^2 size). The primary objective of the study was to compare pharmacokinetics of the two products (oral vs. TDS). The secondary objective was to assess the local tolerability and adhesion of the TDS over a 96-hour wear period (one administration). Skin tolerability was assessed by having the investigator score the site for erythema at 1 hour and at 12 hours after patch removal. The scoring system was as follows:

Score	Rating	Description
0	Absent	No detectable application site
1	Mild	Faint or barely perceptible
2	Moderate	Bright pink or sunburned appearance
3	Severe	Beet red appearance

Eighteen (18) subjects (eight men and 10 women) were randomized. Sixteen completed the study. One withdrew due to her own request (husband in a car accident) and the other (also a female) withdrew due to an AE (headache, nausea, vomiting). Both actually did receive oxybutynin TDS. The results of the erythema scores are seen in Table 27:

Table 27. Erythema scores at 1 hour and 12 hours after system removal in Study O99005

Erythema score	Pre-application N (%)	1 hr post-removal N (%)	12 hrs post-removal N (%)
Absent	15 (83.3%)	4 (23.5%)	9 (52.9%)
Mild	3 (16.7%)	12 (70.6%)	8 (47.1%)
Moderate	0	1 (5.9%)	0
Severe	0	0	0

[57] NDA 21-351 Vol. 47 Listing 14.3.4.1.1.2 on pg. 330-333, 14.3.4.1.2.2 on pg. 357-364, 14.3.4.1.3.2 (1/2 and 2/2) on pg. 390-394, 14.3.4.2.1.2 on pg. 402-405, 14.3.4.2.2.2 on pg. 429-436, and 14.3.4.2.3.2 (1/2 and 2/2) on pg. 462-466.

[58] NDA 21-351 120-Day Safety Update Report Vol. 1.

Medical Officer's Comments

There are only 17 available subjects for post-dosing measurements. This is unclear since 18 subjects received oxybutynin TDS.

Study O99006

This was a randomized, open-label, three-period, crossover study. Subjects were randomized to sequence. The treatments administered were one single dose of oxybutynin TDS (39 cm^2 size). The only differences in periods were that the patch was administered either to the abdomen, buttock or hip. The primary objective of the study was to compare pharmacokinetics (bioequivalence) of the three sites (abdomen vs. buttock vs. hip). The secondary objective was to assess the local tolerability and adhesion of the TDS over a 96-hour wear period (one administration, three different anatomic sites). Skin tolerability was assessed by having the investigator score the site for erythema at 1 hour and at 24 hours after patch removal. The scoring system was as follows:

Score	Rating	Description
0	Absent	No detectable application site
1	Mild	Faint or barely perceptible
2	Moderate	Bright pink or sunburned appearance
3	Severe	Beet red appearance

Twenty-four (24) subjects (11 men and 13 women) were randomized. Each subject received all three treatments. The results of the erythema scores are seen in Tables 28, 29 and 30.

Table 28. Erythema scores at 1 hour and 24 hours after system removal in Study O99006 (abdomen)

Erythema score	Pre-application N (%)	1 hr post-removal N (%)	24 hrs post-removal N (%)
Absent	24 (100%)	15 (63%)	24 (100%)
Mild	0	9 (38%)	0
Moderate	0	0	0
Severe	0	0	0

Table 29. Erythema scores at 1 hour and 24 hours after system removal in Study O99006 (buttock)

Erythema score	Pre-application N (%)	1 hr post-removal N (%)	24 hrs post-removal N (%)
Absent	24 (100%)	17 (71%)	21 (87%)
Mild	0	7 (29%)	3 (13%)
Moderate	0	0	0
Severe	0	0	0

Table 30. Erythema scores at 1 hour and 24 hours after system removal in Study O99006 (hip)

Erythema score	Pre-application N (%)	1 hr post-removal N (%)	24 hrs post-removal N (%)
Absent	24 (100%)	16 (67%)	21 (87%)
Mild	0	8 (33%)	3 (13%)
Moderate	0	0	0
Severe	0	0	0

Medical Officer's Comments

In O99005, skin sites were assessed at 1 and at 12 hours after patch removal. Here, the sites were assessed at 1 and 24 hours after patch removal

Study O99007

This was a randomized, open-label, three-period, crossover study. Subjects were randomized to sequence. The treatments administered were three sequential applications of either:

13 cm^2 oxybutynin TDS

26 cm^2 oxybutynin TDS

39 cm^2 oxybutynin TDS

The first two applications remained in place for 84 hours and the third for 96 hours.

The primary objective of the study was to compare pharmacokinetics (dose-proportionality) of the three sizes of TDS. The secondary objective was to assess the local tolerability and adhesion of the TDS.

Skin tolerability was assessed by having the investigator score the site for erythema immediately after removal, then at 1 hour and at 12 hours after patch removal of the 3rd system. The scoring system was as follows:

Score	Rating	Description
0	Absent	No detectable application site
1	Mild	Faint or barely perceptible
2	Moderate	Bright pink or sunburned appearance
3	Severe	Beet red appearance

Twenty-six (26) subjects (13 men and 13 women) were randomized. Two subjects discontinued prior to completing all three periods. One female subject discontinued during the 39 cm2 treatment period because of an AE (headache, sore throat, hoarseness, and "yeast infection of throat"). Another subject (male) was stopped prior to starting the third treatment period because he was smoking, a violation of protocol. The results of the erythema scores are seen in Tables 31, 32 and 33:

Table 31. Erythema scores immediately after removal and at 1 hour and 12 hours after system removal in Study O99007 (13 cm^2 TDS)

Erythema score	Immediately post-removal N (%)	1 hr post-removal N (%)	12 hrs post-removal N (%)
Absent	11 (42%)	15 (58%)	15 (58%)
Mild	14 (54%)	9 (35%)	7 (27%)
Moderate	0	1 (4%)	3 (12%)
Severe	0	0	0
Missing score	1 (4%)	1 (4%)	1 (4%)

Table 32. Erythema scores immediately after removal and at 1 hour and 12 hours after system removal in Study O99007 (26 cm^2 TDS)

Erythema score	Immediately post-removal N (%)	1 hr post-removal N (%)	12 hrs post-removal N (%)
Absent	9 (38%)	13 (71%)	11 (46%)
Mild	15 (63%)	11 (29%)	11 (46%)
Moderate	0	0	2 (8%)
Severe	0	0	0
Missing	0	0	0

Table 33. Erythema scores immediately after removal and at 1 hour and 12 hours after system removal in Study O99007 (39 cm^2 TDS)

Erythema score	Immediately post-removal N (%)	1 hr post-removal N (%)	12 hrs post-removal N (%)
Absent	14 (54%)	13 (50%)	16 (62%)
Mild	11 (42%)	9 (35%)	7 (27%)
Moderate	0	1 (4%)	1 (4%)
Severe	0	0	0
Missing	0	3 (12%)	2 (8%)

Medical Officer's Comments

It is not clear why data for 3 of the 26 subjects is missing for the oxybutynin 39 cm^2 TDS.
It is not clear why erythema scores appear to worsen slightly with time for the oxybutynin 26 cm^2 TDS.

Study O99009

Part I: Double-Blind Period

The 39 cm^2 patch was not used in this part of the single Phase 3 study. Instead, only 13 cm^2 and 26 cm^2 patches were used. During Part I, skin tolerability assessment and adhesion assessment occurred at Week 3, 6, 9, and 12. During these visits, the adhesion of the current system was assessed and the areas directly beneath previous system applications were visually inspected.

Tolerability of the previously used application sites were rated in terms of the erythema observed at the application sites using the following rating scale. Severe reaction (grade 3) or other intolerability to the system was reported as an AE.

Score	Rating	Description
0	Absent	No detectable application site
1	Mild	Faint or barely perceptible
2	Moderate	Bright pink or sunburned appearance
3	Severe	Beet red appearance

The erythema at the application site assessed by the investigator in Study O99009 at the endpoint of the double-blind period is provided in Table 34.

Table 34. Study O99009 Summary of Erythema at Application Site at Endpoint—Part II (Double-Blind Period)*

Degree of Erythema	Transdermal System											
	13 cm^2 n=510						26 cm^2 n= 510					
	Placebo		Oxybutynin		Overall		Placebo		Oxybutynin		Overall	
	n	%	n	%	n	%	n	%	n	%	n	%
(0)Absent	171	66	120	47.8	291	57.1	186	72.7	108	42.5	294	57.6
(1)Mild	70	27	79	31.5	149	29.2	59	23	92	36.2	151	29.6
(2)Moderate	16	6.2	46	18.3	62	12.2	11	4.3	46	18.1	57	11.2
(3)Severe	2	0.8	6	2.4	8	1.6	0	0	8	3.1	8	1.6

*Table 12.5-1 in Vol. 45 on pg. 116

Part II: Open-Label Dose Titration

The 39 cm^2 TDS was used in the open-label dose titration Part II of the single Phase 3 trial, O99009 and skin tolerability assessments were conducted at pre-determined intervals. Part II was a 12-week open-label, dose titration safety period. All patients began Part II wearing a single 13 cm^2 TDS. The investigators could then titrate the patient's dose up to a single 26 cm^2 or 39 cm^2 TDS during the first four weeks of Part II. The dose remained fixed for the last eight weeks of Part II. During Part II, skin tolerability assessment and adhesion assessment occurred at Week 2, 4, and 12, which were conducted in the same manner as described for Part I.

A total of 411 patients entered Part II and 358 patients completed Part II. At the end of dose titration, 211 patients (51.3%) had been titrated to oxybutynin 39 cm^2 TDS. All patients at the Week 2 skin assessment had been wearing the 13 cm^2 TDS prior to that visit. All patients at the Week 4 skin assessment had been wearing the 13 or 26 cm^2 TDS prior to that visit. The results of the erythema scores at endpoint in Part II is provided in Table 35.

Table 35. Study O99009 Summary of Erythema at Application Site at Endpoint—Part II (Dose-Titration Open-Label Period)*

Degree of Erythema	Transdermal System							
	13 cm^2 n=52		26 cm^2 n= 151		39 cm^2 n=198		Overall n=401	
	n	%	n	%	n	%	n	%
(0)Absent	27	51.9	68	45	87	43.9	182	45.4
(1)Mild	18	34.6	58	38.4	87	43.9	163	40.6
(2)Moderate	7	13.5	23	15.2	24	12.1	54	13.5
(3)Severe	0	0	2	1.3	0	0	2	0.5
Missing	0	0	0	0	0	0	0	0

*Table 12.5-2 in Vol. 45 on pg. 117; Table 14.3.5.6.1.1 in Vol. 49 on pg. 377-379, and Listing 16.2.10.3 in Vol. 113 on pg. 259-450.

Part III: Open-Label Safety Extension
The 39 cm^2 TDS was used in the open-label safety extension Part III of the single Phase 3 trial O99009 and skin tolerability assessments were conducted at pre-determined intervals. Part III was a 28-week open label safety extension with the patients on a single TDS and continued on the same dose as was administered for the final 8 weeks of Part II. During Part III, skin tolerance assessment and adhesion assessment occurred at Week 14 and 28, which were conducted in the same manner as described above for Part I.

A total of 142 patients entered Part III and 115 patients completed Part III. At entry, 75 patients were on the 39 cm^2 TDS. See Table 36 for the summary of erythema at application site at endpoint for Part III.

Table 36. Study O99009 Summary of Erythema at Application Site at Endpoint—Part III (Open-Label Safety Extension Period)*

Degree of Erythema	Transdermal System							
	13 cm^2 n=13		26 cm^2 n= 45		39 cm^2 n=62		Overall n=120	
	n	%	n	%	n	%	n	%
(0)Absent	7	53.8	21	46.7	22	35.5	50	41.7
(1)Mild	4	30.8	19	42.2	35	56.5	58	48.3
(2)Moderate	2	15.4	5	11.1	5	8.1	12	10.0
(3)Severe	0	0.0	0	0.0	0	0.0	0	0.0
Missing	0	0.0	0	0.0	0	0.0	0	0.0

*Table 14.3.5.6.3.1 in Safety Update Vol.1 on pg. 491; Listing 16.2.10.3.2 in Safety Update Vol. 5 on pg. 2142-2162.

Medical Officer's Comment

- **Although severe erythema as determined by the investigator was uncommon, 16 of the 18 severe site reactions in the Study O99009 occurred at the active application sites.**

Skin tolerability data for other trials submitted in this NDA:

Study O96003
The 39 cm^2 TDS was not used in this study. This was a single administration study comparing a 10 cm^2 patch to a 5 mg dose of oral oxybutynin with the primary intent of assessing comparative pK.

Study O96004
The 39 cm^2 TDS was not used in this dermal irritation study. Instead, the 5 cm^2 TDS was used. This was a 14-day, double-blinded, placebo-controlled study in 25 subjects. The objective of the study was to evaluate the incidence and severity of **cumulative skin irritation**. Active and placebo

patches were applied daily (on opposite sides of the same patient) by site personnel. Dermatologic examination was conducted at baseline, immediately following removal of each system (daily), and 24 hours after the removal of the final system. The dermatological evaluation was conducted using the Hill-Top scoring system. The assessors were highly trained personnel using a standard light source. Photographs were taken of the site at baseline, immediately following removal of the first and final system and then 24 hours after removal of the final system.

Study O96005

The 39 cm^2 patch was not used in this Dermal Irritation study. Instead, the 5 cm^2 patch was used. The object of this study was to evaluate the incidence of **contact sensitization** following repetitive applications of the TDS active and placebo patch. In this study, one active and one placebo patch were applied to the same subject three times per week for 21 days (the induction period). The contact time for each application was 24 hours. Systems were applied to the same site each time unless significant irritation developed. A rest period of 10-17 days followed the induction period. Then, a single 24-hour "challenge" application was made using placebo and active on each subject.

Dermal reactions were graded by site personnel prior to application and immediately following removal of each patch. Dermal reactions were also graded at 24 and 48 hours after removal of the challenge patch. The assessing site personnel used the Hill-Top scoring system (Appendix A in Final Study Report), were blinded, were adequately trained, and were using a standardized light source. Photographs were taken prior to and at the time of dermatological evaluation of the challenge.

Medical Officer's Comment

The initial dermatotoxicity studies in healthy volunteers (O99005 and O99006) indicated that the systems could be a mild irritant in normal use but would rarely lead to contact sensitization.

Study O96017

The 39 cm^2 patch was **not** used in this randomized, double-blind, six-week treatment period, dose-titration design, Phase 2 study. Instead, multiples of 13 cm^2 were employed.

One patient in Study O96017 demonstrated contact sensitization to the active TDS. Upon completion of the study, the patient presented with a 1-week history of itchy erythema on abdomen, thighs, and back. The patient agreed to a rechallenge experiment with 3 TDS systems: one active TDS, one placebo TDA, and a matching placebo without the enhancer component. The patient showed a reaction consistent with an allergic contact dermatitis to the active TDS only.

Overview of skin tolerability data:

A total of 3173 application sites were evaluated in 538 patients for skin tolerability in U-UI patients (0-24 weeks) receiving active TDS with erythema scores as follows (Table 10-3 in Vol. 30 on pg. 112):

Absent	1558 (49.1 %);
Mild	539 (36.1 %);
Moderate	443 (14.0 %);
Severe	26 (0.8 %);
Missing	48

The degree of erythema tended to decrease with time after TDS removal (Table 10-1 in Vol. 30, on pg. 110). At one hour after TDS removal in a total of 176 patients, moderate erythema was noted in 4 patients, mild erythema in 79 patients, and no erythema in 93 patients. At 12 hours after TDS removal in 17 patients, mild erythema was noted in 8 patients, and no erythema in 9 patients. At 24 hours after TDS removal in a total of 160 patients, moderate erythema was noted in 4 patients, mild erythema in 34 patients, and no erythema in 120 patients.

Medical Officer's Comment

The application site grading system revealed 26 application sites with severe site erythema (0.8% of 3173 sites evaluated). All degrees of erythema tended to resolve in short order after patch removal.

In terms of the number of treatment-related application site adverse events, 120 of the 542 active TDS patients in the integrated safety studies or 22.1% reported application site reactions. Forty-three (43) out of 542 or 7.9% active TDS patients in the integrated safety studies withdrew prematurely due to application site AEs.

9.8.2 Electrocardiograms

No specific QT study was performed. Overall, no trends toward change in ECG were noted in the clinical studies. Two patients (0132 and 1422) in the O99009 active TDS treatment group had clinically significant treatment-emergent changes (inferior infarct or right atrial enlargement) at endpoint with normal baseline ECGs but did not develop clinical symptoms during their participation in the study. Dependent on treatment group, between 50-64% of the ECGs at endpoint were read as "abnormal, not clinically significant". Tables 9.7-1 and 9.7-2 in Vol. 30 on pg. 107 and Table 11.1 in Vol. 39 on pg. 325-335 were reviewed.

9.8.3 Post-void Residual Urine Volume

Overall, the mean post-void residual urine volume did not change across treatments and time. Tables 12.1, 12.2, and 12.3 in Vol. 39 on pg. 336-356 were reviewed. A residual volume >100 mL was present in 10 patients at the last visit of Study O96017 (3 in the TDS treatment group) and 36 patients in Study O99009 had PVR volumes >150 mL at some point (baseline, baseline and endpoint, or endpoint). No significant increase in post-void residual urine volume was noted with transdermal oxybutynin treatment.

9.9 Adequacy of Patient Exposure and Safety Assessment

The safety profile of the oxybutynin transdermal system is probably adequate for approval with the exception of the lack of a controlled assessment of cumulative irritation potential for the 39 cm^2 system. Skin tolerability issues were noted and a fairly limited safety database was submitted. Much of the safety data is derived from experience with the low (13 cm^2) and middle (26 cm^2) doses. The extensive data previously submitted for oral oxybutynin must be taken into consideration.

The safety database does demonstrate less dry mouth associated with transdermal oxybutynin than reported with oral oxybutynin, however it remains unclear what dose of transdermal oxybutynin is equivalent to any particular dose of oral oxybutynin from an efficacy perspective. The reviewer believes that some of the decreased incidence of dry mouth is due to the use of ineffective doses of oxybutynin in the transdermal groups.

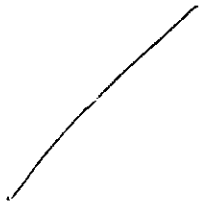
9.10 Safety Findings and Proposed Labeling

The most important safety concern identified during the review of this NDA is skin tolerability. Review of the Package Insert will be completed after oxybutynin TDS is found to be approvable.

10 USE IN SPECIAL POPULATIONS

The sponsor performed standard subset safety analyses for the data from the integrated safety studies based on gender, race, and age. No obvious differences across these groups were identified, however the total percentage of male (8%) and non-Caucasian (8%) patients included in these analyses was small. The geriatric status of the U-UI patients was nearly balanced with approximately 46% being elderly (≥65 years of age).

The pharmacokinetics of oxybutynin TDS was not evaluated in subjects with renal impairment, liver insufficiency, other disease states, or in pediatric subjects. In correspondence dated September 4, 2001 and submitted to NDA 21-351 as Amendment B2, the sponsor requested a partial waiver of pediatric studies in children under the age of six and a deferral of pediatric studies in children aged 6 to 16 inclusive until March 2003. The Pediatric Protocol Synopsis for the deferred study in children aged 6 to 16 inclusive was also submitted and it provided insufficient details to grant the deferral. In a regulatory letter dated October 23, 2001, the partial waiver for pediatric studies for children under the age of six was granted and the sponsor was asked to submit the pediatric protocol with due diligence. Comments and request for information regarding the submitted pediatric protocol synopsis were sent to the sponsor in a second regulatory letter dated October 23, 2001. In correspondence dated December 12, 2001 and submitted to NDA 21-351 as Amendment N000 PU, the sponsor submitted a DRAFT pediatric protocol



Medical Officer's Comment

The proposed pediatric study appears reasonable and eventually, a deferral for starting this study should be granted.

11 PACKAGE INSERT

Review of the Package Insert will be completed after oxybutynin TDS is found to be approvable.

12 CONCLUSIONS AND RECOMMENDATIONS

12.1 Overall Risk-Benefit Analysis

12.1.1 Benefits of Oxytrol ™ Treatment

The sponsor has not provided "substantial evidence" to establish the effectiveness of the oxybutynin transdermal system, as required by Section 505(d) of the Federal Food, Drug, and Cosmetic Act. The sponsor conducted a single adequate and well-controlled efficacy study to support approval, Study O99009. The characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim include a statistically very persuasive finding.[59] Data from Study O99009 demonstrated limited efficacy at best in two endpoints (urinary incontinence episodes and volume voided) and missed in the critical secondary endpoint of urinary frequency after deleting Site #12. Study O99009 was not support by additional evidence. Transdermal oxybutynin was not

[59] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. May 1998, pg 15.

confirmed as being equivalent to oral oxybutynin by blood levels as a result of significantly diminished metabolite concentrations, and lower and less variable C_{max} for the patient. The efficacy of transdermal oxybutynin was not found to be equivalent to oral oxybutynin in the Phase 2 Study **O96017**. This was despite 68% of patients in the TDS group ultimately requiring a dose of 52 cm^2. This 52 cm^2 dose is higher than the maximum dose requested for approval.

The safety database does demonstrate less dry mouth associated with transdermal oxybutynin than reported with oral oxybutynin (i.e. Ditropan), however it remains unclear what dose of transdermal oxybutynin is equivalent to any particular dose of oral oxybutynin from an efficacy perspective. The reviewer believes that some of the decreased incidence of dry mouth is due to the use of ineffective doses of transdermal oxybutynin.

12.1.2 Risks of Oxytrol ™Treatment

It is difficult to compare the risks of the oxybutynin transdermal system to other medical therapeutic options since a limited safety database for the oxybutynin transdermal system was submitted. Skin tolerability is a concern with this transdermal system and is not an issue with approved oral medical therapies for overactive bladder.

12.1.3 Summary of Risk-Benefit Analysis

In the Phase 3 Study **O99009** over the 12-week double-blind treatment period for the **primary efficacy endpoint** of urinary incontinence episodes:

- mean and median change-from-baseline of overactive bladder patients in the oxybutynin 13 cm^2 and 26 cm^2 transdermal system (TDS) groups were not statistically improved compared with the placebo group; the mean and median change-from-baseline in the oxybutynin 26 cm^2 TDS group were actually worse than placebo
- mean change-from-baseline in the oxybutynin 39 cm^2 TDS group was not statistically improved compared with the placebo group
- median change-from-baseline in the oxybutynin 39 cm^2 TDS group patients demonstrated a statistically significant improvement over placebo, however the difference from baseline over placebo was only 4.5 episodes of urinary incontinence per 7 days, or 0.64 episodes per day
- the clinical significance of a median improvement of 4.5 urinary incontinence episodes per week is unclear, especially in light of results from currently approved overactive bladder medical therapies

In Study **O99009** over the 12-week double-blind treatment period for the **secondary efficacy endpoint** of urinary frequency:

- mean and median change-from-baseline in the oxybutynin 13 and 26 cm^2 TDS groups were not statistically improved compared with the placebo group
- mean change-from-baseline in the oxybutynin 39 cm^2 TDS group was not statistically improved compared with the placebo group
- median change-from-baseline in the oxybutynin 39 cm^2 TDS group was not statistically improved compared with the placebo group, when the patients from Site #12 were removed from the analysis

It should be noted that the prespecified Statistical Analysis Plan (SAP) for Study **O99009** was for a parametric ANCOVA analysis (i.e. means), however the sponsor also evaluated the data by non-parametric ranking procedure (i.e. medians) after it was noted that the distributional normality assumption failed to hold for the diary data. Study **O99009** also appeared to be underpowered.

The Phase 2 Study **O96017** failed on its primary efficacy endpoint, equivalence in the responder rate for the oral and transdermal oxybutynin groups, in both the evaluable and intent-to-treat analysis populations, this despite 68% of the patients ending up on a dose of 52 cm^2. Study O96017 also was underpowered.

The **Safety Profile** of the oxybutynin transdermal system is probably adequate for approval, however skin tolerability is a concern and a limited safety database was submitted. In addition, no controlled cumulative irritation study for the 39 cm^2 system was conducted. Application site adverse events were reported by 120 (22%) of the 542 patients receiving transdermal oxybutynin in the integrated safety studies and 43 of these patients withdrew due to application site adverse events. If safety data from when the patients were treated with the ineffective oxybutynin 13 and 26 cm^2 TDS doses were deleted, the remaining safety database for the oxybutynin 39 and 52 cm^2 TDS groups is quite limited. The extensive data previously submitted for oral oxybutynin must be taken into consideration.

The safety database does demonstrate less dry mouth associated with transdermal oxybutynin than reported with oral oxybutynin, however it remains unclear what dose of transdermal oxybutynin is equivalent to any particular dose of oral oxybutynin. The reviewer believes that some of the decreased incidence of dry mouth is due to the use of ineffective doses of oxybutynin in the transdermal groups.

12.2 Major Issues with Regard to Sponsor's Proposed Package Insert

Review of the Package Insert will be completed after oxybutynin TDS is found to be approvable.

12.3 Approvability

12.3.1 General Recommendation

It is recommended that the oxybutynin transdermal system (NDA 21-351) receive a not approvable action, based on inadequate efficacy demonstrated in the Primary Clinical Studies O99009 (Phase 3) and O96017 (Phase 2).

12.3.2 Specific Recommendations

- Prior to approval of oxybutynin transdermal for use in the overactive bladder population, the sponsor will need to provide additional evidence of efficacy from at least one new Phase 3 trial.
- Sponsor to consider increasing the dose beyond the proposed oxybutynin 39 cm^2 TDS to increase the efficacy.
- Sponsor is advised to explore options for decreasing the TDS size.
- In any future resubmission of Study **O99009**, the data should be reanalyzed for the ITT population, excluding data from Site #12, excluding data for Subjects #2105 and #2122, and utilizing the correctly transcribed urinary diaries and the correct baseline urinary diaries efficacy data.

cc: Division File System NDA 21-351
HFD-580: D. Shames/ S. Slaughters/ M. Hirsch/ Y. Choi/S. Wang/B. Gierhart/ E. Farinas

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/s/

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3/27/02 09:37:27 AM
MEDICAL OFFICER

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I concur.