CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

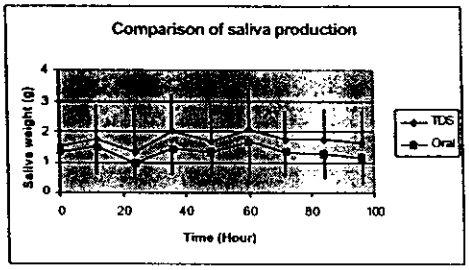
21-351

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-351
Brand Name	Oxytrol ™
Drug Class	Anticholinergic
Drug Substance	Oxybutynin
Drug Product(s)	Oxybutynin trandermal system 3.9 mg/day, 39cm^2
Dosing regimen	The recommended dose is one 3.9 mg/day system applied twice weekly (every 3-4 days).
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Sponsor	Watson Laboratories, Inc.
Type of submission	Amendment to a pending application
Date of submission	8/29/2002
Medical Division	HFD-580 (Division of reproductive and urologic drug products)
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB division	OCPB/DPE-2 (HFD-870)

Dry mouth is the major adverse effect of oxybutynin. Saliva production at steady state after application of TDS appeared greater than that after oral administration of Ditropan XL. This observation may be related to systemic exposure of the less active metabolite, i.e., DEO available after administration of TDS than that after Ditropan XL.



(2) Adhesion data for 3.9 mg/day system from Study O01009: Among 65 applications, 62 appeared well attached (over 90 % of surface area) and 3 cases were partially detached (75-90 % of surface area). This result is similar to that shown in the original submission, in which 95 –98 % appeared good adherence for the overall TDS (i.e., 1.3, 2.6, and 3.9 mg/day systems)

(3) Delivery rates from the two CIA studies were as follows:

Alternative application (Abdomen and buttock)	2.93 – 3.45 mg/ day after first application on abdomen	3.62 – 4.03 mg/day after 6th application on buttock
Keep applying only on abdomen	2.63 –3.09 mg/day after first application	4.72 – 5.93 mg/day after 6th application on abdomen

It was noted that the delivery rate of OXY by alternative application was comparable to the data obtained in the original submission (2.99 – 3.96 mg/day).

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II completed the review of NDA 21-351 resubmitted on 8/29/2002. The clinical pharmacology and biopharmaceutics data in the human pharmacokinetics and biopharmaceutics section of the present NDA resubmission is acceptable. The labeling changes have been conveyed and changes are acceptable.

II. Table of Contents

III. Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

Watson Laboratories, Inc. resubmitted NDA 21-351 for Oxytol ™, oxybutynin transdermal system (TDS), seeking approval for TDS with oxybutynin (OXY) delivery rates of 3.9 mg/day for treatment of patients with overly active bladder with symptoms of urge urinary incontinence, urgency, and frequency.

The drug substance, OXY, is an anticholinergic agent. OXY is known to be well absorbed following oral administration, but undergoes extensive pre-systemic metabolism. The resulting oral bioavailability is less than 10% compared to intravenous dosing. N-desethyloxybutynin (DEO) is the primary circulating active metabolite and is present in plasma at concentrations approximately five times that of the parent compound. Both OXY and DEO undergo rapid metabolism and excretion, with half-lives of approximately 2 hours. The resulting large peak to trough concentration changes within the dosing interval and metabolic profile may contribute to the poor tolerability of the compound.

III-1. Findings from the original submission

The sponsor conducted four pharmacokinetic (PK) studies (three single dose and one multiple dose for two weeks) and two clinical studies (one dose titration and one safety study).

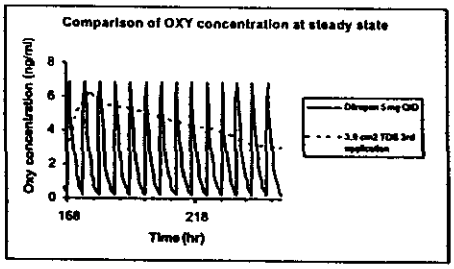
The human pharmacokinetics and biopharmaceutics section includes the results from the four PK studies as well as population PK data from two clinical trials. In addition to those information, *in vitro* skin permeation, drug release, and stability data were reported.

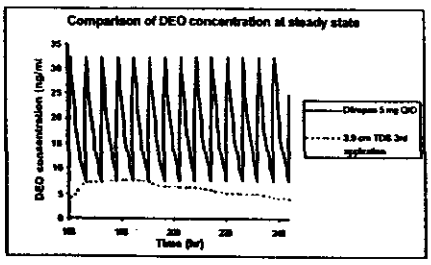
Based upon reviewing the data from a PK perspective, the important findings, potential issues, as well as reviewer's opinion on the management of those potential issues are summarized as follows:

1. From a pharmacokinetic perspective, the clinical pharmacology and biopharmaceutics (CPB) data submitted in the human pharmacokinetics and biopharmaceutics section of the present NDA is acceptable. The sponsor adequately described the pharmacokinetics of oxybutynin (OXY), N-desoxybutynin (DEO; an active metabolite), and stereoisomers.

2. It should be noted that an exposure-response relationship of OXY or DEO after application of TDS was not explored. The sponsor was seeking an appropriate dose of TDS to maintain a comparable systemic exposure of OXY to that after administration of Ditropan 5 mg QID.

3. For OXY, a comparable Cmax (6.6 ng/ml vs 7.4 ng/ml) and larger AUC (408 vs. 224 ng.hr/min) were predicted following TDS 3.9 mg/day system every 96 hours compared to those following oral administration of 5 mg Ditropan QID (See the following figures: Left panel).





4. Of special interest is, however, the substantially less systemic exposure (4-6 times less) of DEO following the application of 3.9 mg/day TDS compared to Ditropan 5 mg (See the following figures: Right panel; Cmax 8.5 ng/ml vs. 41.0 ng/ml and AUC 561 vs 2528

ng.hr/min). DEO is known to have equal pharmacological activity to OXY. Therefore, a poor efficacy as well as less adverse events, if any, may be due to the significantly less exposure to DEO.

5. Other important findings are:

- OXY is delivered consistently during the wearing period for up to 4 days with delivery rate of 0.1 mg /cm^2/day (3.9 mg/day for the 39 cm^2 patch).
- The delivery rate is proportional to the active surface size.
- Systemic exposure to OXY following administration on abdomen is not significantly different from buttock, and hip.
- Steady state reached after second application of TDS. Steady state AUC and Cmax was 1.6 and 1.9 times higher than that after first application, respectively, indicating 60 and 90 % accumulation.
- The demographic characteristics, such as gender, age, and weight, appeared to not significantly affect pharmacokinetics of OXY and DEO following TDS application.
- In Phase I studies, during the wearing period of 84-96 hours, 19 out of 329 application did not appropriately adhere on the application site, i.e., more than 25 % of the active surface was detached. The patient information insert appeared to appropriately describe the treatment when the patch partially or completely falls off, i.e., press it back in place or apply a new patch in a different area. (See the proposed Patient Information Insert)
- The dissolution method and specifications are as follows:

Proposed parameters for the drug release methodology

Variable	Parameters
Apparatus Type	
Dissolution Medium	
Volume of Medium	
Temperature of Medium	
Speed of Rotation	
Sample Pull Times	
Sample Volume	
Units Tested	

Specification [Agency's recommendation (% label claim)]	
	Not less than

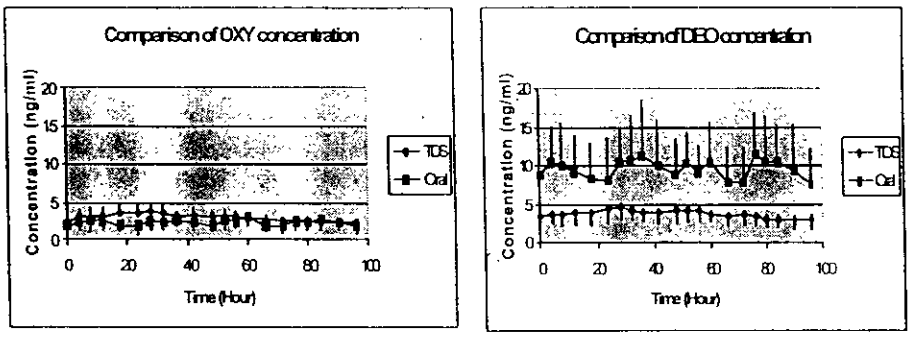
Note that the above method and specifications were accepted by the sponsor on 3/18/2002

III-2. Findings from the present submission

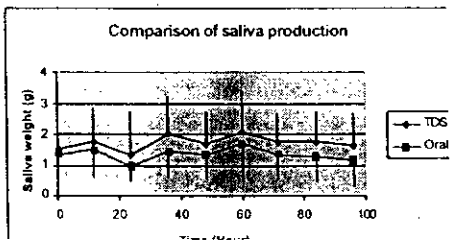
1. From the results of the new comparative pharmacokinetic study, TDS treatment lead to comparable OXY and less DEO exposure compared to Ditropan XL (Refer to the following Table 1).

For OXY, a comparable Cmax at steady state (4.2 ng/ml vs 4.0 ng/ml) and larger AUC0-84 hr at steady state (259 vs. 194 ng.hr/min) were observed following TDS 3.9 mg/day system every 84 hours compared to those following oral administration of 10 mg Ditropan XL once a day. Of special concern is, however, the substantially less systemic exposure (less than the half) of DEO following the application of 3.9 mg/day TDS compared to Ditropan XL (Cmax 4.9 ng/ml vs. 15.2 ng/ml and AUC 321 vs 802 ng.hr/min).This result is

similar to the predicted steady state plasma concentration by a simulation in the original review.



Saliva production after application of TDS is greater than that after oral administration of Ditropan XL. This observation seems related to the less active moieties (i.e., OXY + DEO) available after administration of TDS than that after Ditropan XL.



2. Adhesion data for 3.9 mg/day system from Study O01009: Among 65 applications, 62 appeared good (over 90 % of surface area) and 3 cases were partially detached (75-90 % of surface area). This result is similar to that shown in the original submission, in which 95 –98 % appeared good adherence for the overall TDS (i.e., 1.3, 2.6, and 3.9 mg/day system)

3. Delivery rates from the two cumulative irritation (CIA) dermotoxicity studies were as follows:

Alternative application (Abdo. And buttock)	2.93 – 3.45 mg/ day after first application on abdo	3.62 – 4.03 mg/day after 6th application on buttock
Keep applying only on abdomen	2.63 –3.09 mg/day after first application	4.72 – 5.93 mg/day after 6th application on abdo

It is noted that the delivery rate was 2.99 – 3.96 mg/day in the original submission.

It is noted that the application was every 84 hours for both alternative and same site.

Table1. Steady state Oxybutynin and DEO pharmacokinetic parameters following application of a 39 cm^2 Oxybutynin TDS and oral administration of Ditropan XL (10 mg of oxybutynin tablet QD) (Protocol O01009)

PK Parameter	Descriptive Statistic	Oxybutynin TDS 3.9 /day		Ditropan XL tablet (10 mg/day)	
		Oxy	DEO	Oxy	DEO
C_{max} (ng/ml)	Mean ± SD	4.2 ± 1.0	4.9 ± 2.0	4.0±1.5	15.2±6.7
	CV%	24.6	40.3	37.8	44.0
	Range				
C_{min} (ng/ml) (0-96 hours)	Mean ± SD	2.1±0.3	2.8±1.1	1.3±0.7	5.5±4.1
	CV%	15.5	39.1	56.0	73.9
	Range				
AUC_{0-84} (ng·hr/ml)	Mean ± SD	259±57	321±114	194±68	802±369
	CV%	21.9	35.4	35.1	46.0
	Range				
T_{max} (hours)	Median	28.1	28.1	52.1	48.1
	Mean ± SD	33.3±13.1	31.9±16.6	53.6±27.1	46.8±27.9
	CV%	39.3	51.9	52.1	59.6
	Range				
Fluctuation index	Mean ± SD	0.7±0.2	0.5±0.1	1.3±0.5	1.1±0.4
	CV%	25.4	26.5	39.0	34.3
	Range				

Question Based Review

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Background Information

Oxybutynin (OXY) is a prescribed medication that is indicated for the relief of urinary symptoms of incontinence and urgency associated with detrusor instability.

The drug was first approved for use in the United States in July 1975. The recommended dose is oxybutynin chloride 5 mg, as tablet or syrup, administered 2 to 3 times daily.

Treatment is associated with a high incidence of anticholinergic adverse effects, particularly dry mouth, decreased sweating, and mydriasis with poor accommodation. For many patients, these side effects limit their ability to use the product effectively. Larger doses of oxybutynin, up to 40 mg/day, have been used in patients able to tolerate the associated anticholinergic effects, as well as alternate methods of administration, specifically, direct installation of oxybutynin solutions into the urinary bladder.

OXY is known to be well absorbed following oral administration, but undergoes extensive pre-systemic metabolism. The resulting oral bioavailability is less than 10% compared to intravenous dosing. N-desethyloxybutynin (DEO) is the primary circulating active metabolite and is present in plasma at concentrations approximately five times that of the parent compound. Both OXY and DEO undergo rapid metabolism and excretion, with half-lives of approximately 2 hours. The resulting large peak to trough concentration changes within the dosing interval and metabolic profile may contribute to the poor tolerability of the compound.

Watson Laboratories, Inc. has developed Oxytol ™, oxybutynin transdermal system (TDS), seeking for approval for TDS with oxybutynin delivery rates of 3.9 mg/day for treatment of patients with overly active bladder with symptoms of urge urinary incontinence, urgency, and frequency.

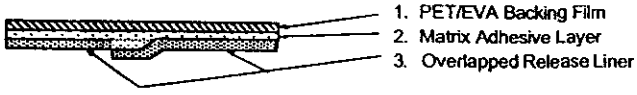
Oxybutynin TDS is an adhesive matrix transdermal system designed for the continuous administration of oxybutynin over a 3-4 day period (See following table for composition of the formulation).

The sponsor expected that transdermal delivery offers several possible advantages over oral administration:

- The dosing interval is prolonged, leading to increased patient compliance and convenience.
- Pre-systemic metabolism may be avoided, leading to lower concentrations of the metabolite, which may improve tolerability.
- The continuous delivery of medication avoids the peaks that follow oral dosing that may also improve tolerability.

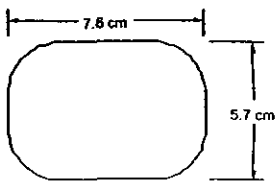
Diagram of the TDS system

Side View



Top View

39 cm^2 System Dimensions



Composition of the Oxybutynin TDS Matrix Adhesive Layer

The nominal and quantitative compositions of the 39 cm^2 oxybutynin adhesive matrix systems used in PK/clinical studies are outlined in the following table. The composition of the to-be-marketed formulation are identical to the formulation used in PK/clinical studies.

Nominal composition of the adhesive matrix for the oxybutynin transdermal systems used in PK studies

Component	39 cm^2 TDS	
	mg/system	% of matrix
Acrylic Adhesive		
Triacetin, USP		
Oxybutynin Base	36	
Total Weight of Adhesive Matrix		

Quantitative composition of Oxybutynin Trandermal Systems

Descrition of layers	Thickness	Mg/cm2	Mg/39 cm2 TDS
Backing film			
Oxybutynin			36.0
Triacetin. USP			
acrylic adhesive			
Release liner			
Total			

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General Attributes of the submission and the present review

In support of the approval of NDA21-351, the sponsor originally submitted the results of four pharmacokinetic (PK) studies (three single dose and one multiple dose for two weeks) and two clinical studies (one dose titration and one safety study). It appeared acceptable from clinical pharmacology and biopharmaceutics perspective provided the appropriate change in labeling. However, mainly due to the lack of efficacy, the non-approval action letter was issued (Refer to the action letter dated 3/26/02)

[redacted] 3.9 mg/day system. In response to the action letter dated on 3/26/02 and to support the approval of 3.9 mg/day TDS, the sponsor additionally submitted the following information on 8/29/2002:

(1) One new clinical study (Study #O 00011) and results of analyses of Study O99009
(2) Two cumulative irritation (CIA) dermotoxicity studies (O02008, and O02009)
(3) A new pharmacokinetic (PK) study (Study #O01009)

From Clinical Pharmacology and Biopharmaceutics perspectives, OCPB review focused only on:

(1) The new PK study (Study #O1009), in which the sponsor compared the steady state PK and metabolism of oxybutynin following transdermal (3.9 mg/day system) and oral administration (Ditropan XL, once-a-day extended release tablet of 10 mg oxybutynin) in healthy volunteers (n=13 for PK). The sponsor also assessed saliva output as a marker for adverse effect
(2) Adhesion data for 3.9 mg/day system
(3) Delivery rate results from two CIA studies

Detailed review on the following issues are available in the original Clinical Pharmacology and Biopharmaceutics review dated 3/22/02:

General clinical pharmacology
Systemic exposure after single dose
Systemic exposure after multiple dose
Dose proportionality
Comparison of systemic exposure of OXY and DEO after multiple dose
Bioavailability / Bioequivalence at different application site
Stereoselective metabolism and its impact on the systemic exposure
Gender effect
In vivo adhesion
Delivery rate following application of TDS
General Biopharmaceutics (Dissolution)

It may be of interest to note following:
For Ditropan XL, the approved dose is 5 mg/day to start and can go up as high as 30 mg/day. While in the present submission, the sponsor is pursuing only 1 size patch (i.e., 3.9 mg/day TDS system) for approval that seems comparable to 10-15 mg/day of Ditropan XL for parent and lower systemic exposure for metabolite. It seems very borderline efficacious.

Comparison of systemic exposure of OXY and DEO after multiple dose

How are the systemic exposure of OXY and DEO compared ?

The sponsor compared the steady state pharmacokinetics of oxybutynin and its metabolite following transdermal (3.9 mg/day system) and oral administration (Ditropan XL, once-a-day extended release tablet of 10 mg oxybutynin) in healthy volunteers (Study #O1009). The sponsor also assessed saliva output as a marker for adverse effect

The study was a randomized, open label, two-way crossover design. Subjects (n=15 enrolled; 13 completed) received two treatments in a randomized sequence.

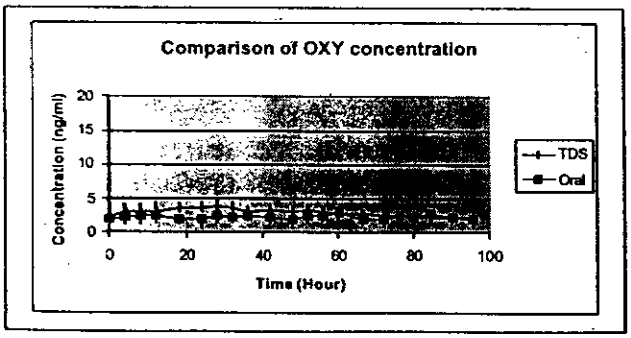
Treatment A: Oxybutynin transdermal systems were applied to the lower abdomen. A baseline blood sample was collected and the first system applied for 84 hours. Upon removal of the first system, subjects were sequestered for 96 hours at the study site to facilitate the collection of the blood and saliva samples and the second system was applied to the opposite site of the lower abdomen for 96 hours. Serial blood samples were collected (See the graph for the collection time).

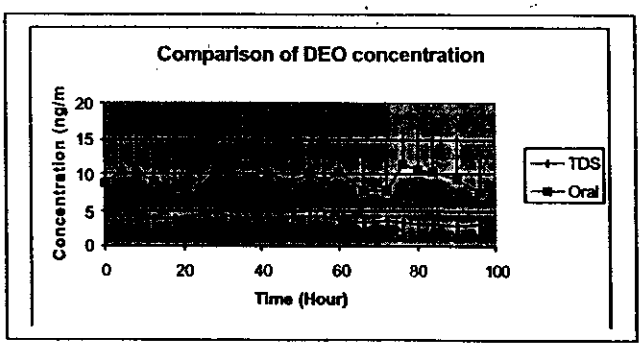
Treatment B: Total six Ditropan XL Extended Release tablets were sequentially administered orally at 24 hour interval. Blood samples for analysis of plasma oxybutynin and DEO concentrations were collected at predetermined time (See the graph for the collection time).

Assessment of saliva output: Saliva output was assessed at the screening visit and at 0, 12, 24, 35, 48, 60, 72, 84, and 96 hours after application of the second Oxy TDS and at the same time after the administration of the 3rd Ditropan XL tablet. At the specified time, each subject rinsed the mouth with approximately 2 ounces of tap water, expectorating the water after rinsing. Ten minutes later, the subject swallowed and saliva in their mouth's and an accurately weighed 1" x 1" square of Parafilm was placed on the tongue. The subjects then chewed Parafilm for 2 minutes after which any accumulated saliva and the chewed Parafilm was expectorated into a previously weighed clear, dry receptacle and the receptacle was weighed again.

Comparison of oxybutynin and DEO systemic exposure

For OXY, a comparable Cmax at steady state (4.2 ng/ml vs 4.0 ng/ml) and larger AUC0-84 hr at steady state (259 vs. 194 ng.hr/min) were observed following TDS 3.9 mg/day system every 84 hours compared to those following oral administration of 10 mg Ditropan XL once a day. Of special concern is, however, the substantially less systemic exposure (less than the half) of DEO following the application of 3.9 mg/day TDS compared to Ditropan XL (Cmax 4.9 ng/ml vs. 15.2 ng/ml and AUC 321 vs 802 ng.hr/min).This result is similar to the predicted result by a simulation at the original review.





Comparison of saliva output:

Saliva production after application of TDS is greater than that after oral administration of Ditropan XL. This observation may be related to the less active metabolite, i.e., DEO available after administration of TDS than that after Ditropan XL.

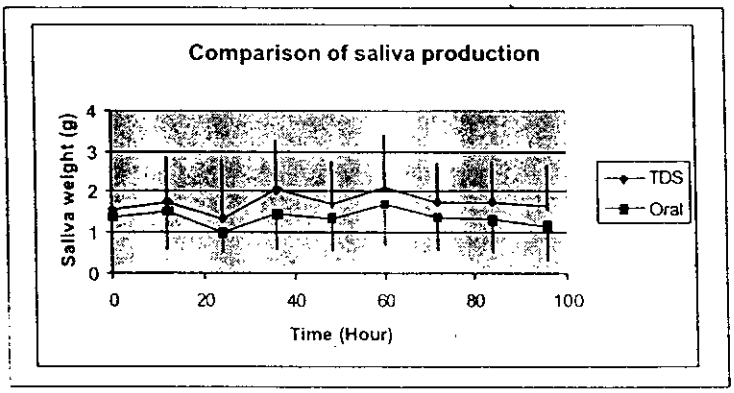


Table I. Steady state Oxybutynin and DEO pharmacokinetic parameters following application of a 39 cm^2 Oxybutynin TDS and oral administration of Ditropan XL (10 mg of oxybutynin tablet QD) (Protocol O01009)

PK Parameter	Descriptive Statistic	Oxybutynin TDS 3.9 /day		Ditropan XL tablet (10 mg/day)	
		Oxy	DEO	Oxy	DEO
C_{max} (ng/ml)	Mean ± SD CV% Range	4.2 ± 1.0 24.6	4.9 ± 2.0 40.3	4.0±1.5 37.8	15.2±6.7 44.0
C_{min} (ng/ml) (0-96 hours)	Mean ± SD CV% Range	2.1±0.3 15.5	2.8±1.1 39.1	1.3±0.7 56.0	5.5±4.1 73.9
AUC_{0-84} (ng·hr/ml)	Mean ± SD CV% Range	259±57 21.9	321±114 35.4	194±68 35.1	802±369 46.0
T_{max} (hours)	Median Mean ± SD CV% Range	28.1 33.3±13.1 39.3	28.1 31.9±16.6 51.9	52.1 53.6±27.1 52.1	48.1 46.8±27.9 59.6
Flucuation index	Mean ± SD CV% Range	0.7±0.2 25.4	0.5±0.1 26.5	1.3±0.5 39.0	1.1±0.4 34.3

Comparison of plasma R-and S-oxybutynin and DEO pharmacokientics

In both treatments A (TDS) and B (Oral), the systemic exposure of R-oxybutynin appeared less than S-oxybutynin (See Table II). This difference may be due to the more extensive metabolism of R-oxybutynin, since the formation of R-DEO appeared to be higher than that of S-DEO.

In between treatment A (TDS) and B (Oral), mean R-oxybutynin Cmax and AUC0-84 were approximately 33 and 76 % greater, respectively, with treatment A (TDS) compared to treatment B(Oral). In contrast, mean R-DEO Cmax and AUC 0-84 were approximately 69 and 59 % less, respectively, with treatment A compared to treatment B.

Table II. Steady state Oxybutynin and DEO pharmacokinetic parameters following application of a 39 cm^2 Oxybutynin TDS and oral administration of Ditropan XL (10 mg of oxybutynin tablet QD) (Protocol O01009)

PK Parameter	Descriptive Statistic	Oxybutynin TDS 3.9 /day				Ditropan XL tablet (10 mg/day)			
		R-oxy	S-oxy	R-DEO	S-DEO	R-oxy	S-oxy	R-DEO	S-DEO
C_{max} (ng/ml)	Mean ± SD	1.6±0.3	2.3±0.7	2.3±0.6	2.1±0.8	1.2±0.7	2.3±1.0	7.4±3.4	5.7±2.6
	CV%	20.7	27.9	26.1	35.9	58.0	44.7	45.7	45.1
	Range								
C_{min} (ng/ml) (0-96 hours)	Mean ± SD	0.8±0.2	1.1±0.1	1.4±0.5	1.2±0.4	0.4±0.2	0.8±0.5	2.9±2.6	2.5±1.8
	CV%	19.0	13.0	36.9	33.3	61.3	58.3	89.8	72.5
	Range								
AUC_{0-84} (ng·hr/ml)	Mean ± SD	104±17	144±31	162±45	146±52	59±30	117±52	399±237	334±173
	CV%	16.7	21.2	27.6	35.6	50.3	44.4	59.3	51.7
	Range								
T_{max} (hours)	Median	21.1	21.1	21.1	36.1	60.1	30.1	10.1	6.1
	Mean ± SD	24.6±15.4	28.3±21.0	30.2±26.3	32.6±22.5	48.4±37	40.8±35.1	24.8±30.4	19.2±26.6
	CV%	62.8	74.3	87.1	69.0	76.5	86.2	126.3	138.3
	Range								
Flucuation index	Mean ± SD	0.6±0.2	0.7±0.2	0.5±0.1	0.5±0.1	1.2±0.4	1.2±0.5	1.1±0.5	1.0±0.6
	CV%	26.4	33.5	24.0	17.2	36.2	42.4	47.4	59.3
	Range								

Correlation of oxybutynin or DEO with saliva output

A non-significant correlation was found between the paired differences in the average plasma oxybutynin concentration and the total amount of saliva produced. In contrast, a stronger correlation was found between the paired differences in the average DEO concentration and the total amount of saliva produced.

Similarly, a non-significant correlation was found between the paired differences in the average plasma R-oxybutynin concentrations and the total amount of saliva produced. In contrast, a stronger correlation was found between the paired differences in the average plasma R-DEO concentrations and the total amount of saliva produced.

Oxybutynin is an anticholinergic agent, which is effective in treating urinary incontinence and produces anticholinergic side effect such as dry mouth. The principal cause of this side effect is believed to be DEO, the major active metabolite, and more specifically, the R-isomer of DEO.

The present correlation is supportive to the above hypothesis that the cause of the dry mouth be the active metabolite of oxybutynin.

In vivo adhesion

Is there any detachment of the TDS from the application site during the suggested wearing duration?

Because of the long duration of application of TDS, i.e., 3-4 days of application on the skin, it is important to ensure that the TDS is not detached during the wearing period.

The number of partial and complete transdermal system detachments for Oxybutynin TDS were reported in six studies (O96003, O96017, O99005, O99006, O99007, O99009). System adhesion was verified during each of these six studies by observation of the application site by study site personnel at each study visit. System adhesion was rated as good to excellent in all studies in which adhesion was evaluated.

The adhesion of Oxybutynin TDS as reported in the four pharmacokinetic, the one efficacy, and the one safety and efficacy trial are summarized in the following table.

Adhesion of Oxybutynin TDS

Protocol #	# of Subjects	Total # of System Applications	# of Good to Excellent Attachments[a]	# of Partial Detachments[b]	# of Complete Detachments
Phase I Studies					
O96003	16	15	15	0	0
O99005	18	17	17	0	0
O99006	24	72	71	1	0
O99007	26	225	207	17	1
Phase II / III Studies					
O96017	76	225	219	3	3
O99009[c]	515	3755	3712	21	25

[a] Good to excellent attachment includes an adhesion range of greater than or equal to 75% of the surface area of the system being applied to the skin.
[b] Partial detachment includes an adhesion range of less than 75% of the system surface area of the system being applied to the skin but not complete detachment from the skin.
[c] System applications during the double-blind portion of the study only.

Adhesion scores of ≥ 75% represent good to excellent adhesion and would be expected to be associated with appropriate transdermal delivery of oxybutynin. Adhesion assessments of < 74% may be associated with lower amounts of delivered drug or with individuals unable to appropriately use the transdermal system. Of the 329 Oxybutynin TDS applied during the 4 Phase I pharmacokinetic studies, 1 (0.3%) became completely detached, and 17 (5%) became partially detached. Thus, the adherence of 95% (311/329) of the Oxybutynin TDS applications in these four pharmacokinetic studies were rated as ≥ 75% adhered to the skin and would be expected to perform as anticipated.

Adhesion was only periodically evaluated during the Phase II and III studies. Of the 3980 Oxybutynin TDS applications in the Phase II and III trials, 25 (0.6%) were observed at clinic visits to have became completely detached and 24 (0.6%) became partially detached during routine clinical use. Similar to the pharmacokinetic studies, > 98% of the systems applied in the Phase II and III studies were assessed as being ≥ 75% attached and thus would be expected to perform as anticipated.

In the present resubmission, the sponsor provided additional data from the four studies, i.e., OnO00011, two cumulative irritation (CIA) dermotoxicity studies (O02008, and O02009), and Study O01009.

The results are as follows:

Protocol #	# of Subjects	Total # of System Applications	# of Good to Excellent Attachments[a]	# of Partial Detachments[b]	# of Complete Detachments
O01009	13	65	62	3	0
O00011	121	993	979	14	0
O02008	27	157	148	1	8
O02009	30	169	163	1	5

[a] Good to excellent attachment includes an adhesion range of greater than or equal to 75% of the surface area of the system being applied to the skin.

[b] Partial detachment includes an adhesion range of less than 75% of the system surface area of the system being applied to the skin but not complete detachment from the skin.

This reviewer is of the opinion that the adhesion performance is acceptable and the patient information insert appeared to appropriately describe the treatment when the patch partially or completely fall off, i.e., press it back in the same place or apply a new patch in a different area. (See the proposed Patient Information Insert)

Delivery rate following application of TDS

What was the delivery rate of oxybutynin following application of TDS?

Because relatively large amount of OXY (36 mg) is loaded in a 3.9 mg/day system, it is of importance to investigate the delivery rate and ensure no dose-dumping that may results in sudden high systemic exposure.

The sponsor investigated the delivery rate based on the residual contents of OXY after application of TDS as follows:
Residual oxybutynin content was measured in worn systems in the pharmacokinetic studies. System depletion data were not obtained in the Phase II and III studies.

The estimated amount of oxybutynin delivered was calculated as the difference between the analyzed residual content of the used systems and the mean value of the unused control system.

Based on data from the residual content analysis of the used systems (n=291; Studies O99005, O99006 and O99007), the nominal oxybutynin delivery rate was 0.10 ± 0.02mg/cm^2 system surface area/24 hours.

In the present resubmission, the sponsor provided the additional delivery rate data from Two cumulative irritation (CIA) dermotoxicity studies (O02008, and O02009). The results are as follows:

Alternative application (Abdo. And buttock)	2.93 – 3.45 mg/ day after first application on abdomen	3.62 – 4.03 mg/day after 6th application on buttock
Keep applying only on abdomen	2.63 –3.09 mg/day after first application	4.72 – 5.93 mg/day after 6th application on abdomen

It is noted that the delivery rate was 2.99 – 3.96 mg/day in the original submission (Refer to the original Clinical Pharmacology and Biopharmacetuics review).

This reviewer is of the opinion that the delivery rate estimation is acceptable considering the relatively steadily maintained plasma concentration without any evidence of dose-dumping. Due to the increased delivery rate by applying on the same site, it should be noted in the label that the TDS should not be applied consecutively at the same site. It is noted that the package insert and Patient information instructed the application appropriately.

Dissolution

Drug release specifications for oxybutynin were established using data for 24 batches of Oxybutynin TDS. The mean ± SD of the oxybutynin assay data at batch release and on stability for systems stored at 25°C/60%RH corresponded to 98 ± 2 % of the label claim. The data were within the proposed product specifications of the label claim — for oxybutynin.

The results of drug release testing for the Oxybutynin TDS used in the pharmacokinetic studies and the efficacy and safety trials are as follows:

Oxybutynin TDS drug release data from pharmacokinetic and clinical study batches

Protocol Number	Code/Control Number	Nominal Oxybutynin Delivery Rate (mg/day)	Oxybutynin Release Average % Label Claim (range of individual values)		
O96003	0063-1/95Z174	1.4	58	87 (	101
O96017	0140-0/97Z002	1.3	47	71 (	94
O99005	0352-0/99Z137	3.9	43	75	96
O99006	0352-0/99Z137	3.9	43	75 (	96
O99007	0350-0/00Z133	1.3	37	67 (	90
	0351-0/99Z143	2.6	43 (	75	97
	0352-0/99Z137	3.9	43	75 (	96
O99009	0350-0/99Z173	1.3	42	76 (	93
	0351-0/99Z178	2.6	44	79	95
	0351-0/99Z162	2.6	43 (	76 (	96
	0352-0/99Z183	3.9	44	76	96
	0352-0/99Z167	3.9	45	79	98

Oxybutynin release was rapid with more than — of the total system content delivered in vitro within approximately — The release profiles measured at — s for 39 cm^2 systems stored under standard temperature (25°C) and humidity (60%) conditions were virtually identical to those measured at zero time, indicating that system performance remained consistent over this storage interval . Additionally, no decrease in oxybutynin and triacetin content was observed during — storage period.

Data for 13 cm^2 and 26 cm^2 systems are available for storage duration's up to — respectively. Release profiles for these 13 and 26 cm^2 systems were indistinguishable from the 39 cm^2 system profiles under comparable storage conditions and times.

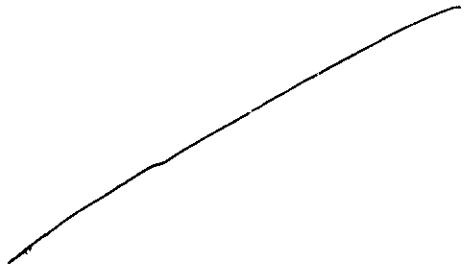
As seen with the 39 cm^2 systems , no decrease in oxybutynin and triacetin content was observed during the — week storage periods. The conclusions reached for the — data thus apply equally to the data over — supporting a proposed shelf-life of at least 2 years for this product.

In vitro oxybutynin release profiles for 39 cm^2 Oxybutynin TDS after — storage at 25°C and 60% relative humidity (system control number 99Z137)

Oxybutynin TDS oxybutynin and triacetin content over time under storage conditions of 25°C and 60% relative humidity

Protocol(s)	Control Number	System Size	Time (weeks in storage)	Oxybutynin Content (mg/system)	Triacetin Content (mg/system)
O96017	97Z002	13			

O99007 O99009	99Z143	26	
O99005 O99006 O99007	99Z137	39	



Reviewer's comment on the dissolution specification:

The sponsor agreed the agency's following dissolution specifications (Refer to the letter from the sponsor dated 3/18/2002).

	Agency's recommendation % label claim	Sponsor's proposal % label claim
	Not less than	Not less than

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27 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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2. SYNOPSIS

Name of Sponsor/Company: Watson Laboratories, Inc., Salt Lake City, Utah 84108	**Location of Full Report in the Submission**	*(For National Authority Use only)*
Name of Finished Product: Oxybutynin Transdermal System	**Volume:**	
Name of Active Ingredient(s): Oxybutynin	**Page:**	

Title of Study: Oxybutynin and N-Desethyloxybutynin Steady-State Pharmacokinetics Following Transdermal and Oral Administration in Healthy Volunteers

Investigator: —

Study Center: —

Studied period (years): 2001
(date of first enrollment): 15 October, 2001
(date of last completed): 06 November 2001

Phase of development: Phase IIIb

Objectives: The primary objective of this study was to compare the steady-state pharmacokinetics and metabolism of oxybutynin following transdermal and oral administration. Secondary objectives of the study were: 1) to assess oxybutynin's affect on saliva output, 2) evaluate the adhesion properties of the transdermal system, and 3) to further evaluate oxybutynin's safety.

Methodology: This study was a randomized, open-label, two-way crossover design. Subjects received two treatments (Treatment A and B) in a randomized sequence (A/B or B/A) with each subject receiving each study treatment once.

During Treatment A, oxybutynin transdermal systems (Oxy TDS) were sequentially applied to the lower abdomen. A baseline blood sample was collected and the first system applied for 84 hours. Upon removal of the first system, subjects were sequestered for 96 hours at the study site to facilitate the collection of blood and saliva samples and the second system was applied to the opposite side of the lower abdomen for 96 hours. Serial blood samples for analysis of plasma oxybutynin and N-desethyloxybutynin (DEO) concentrations were collected over the 180 hours following application of the first system. Assessment of saliva output was conducted at predetermined intervals over the 96 hours after application of the second system.

During Treatment B, six Ditropan XL® Extended Release tablets were sequentially administered orally at 24 hour intervals. Blood samples for analysis of plasma oxybutynin and DEO concentrations were collected at predefined times over the 144 hours after administration of the first tablet. Assessment of saliva output was conducted at predetermined intervals over the 96 hours after administration of the third tablet. Subjects were sequestered for the 96 hours after administration of the third tablet at the study site to facilitate the collection of blood and saliva samples. All other blood collections were done on an out-patient basis.

Number of subjects (planned and analyzed): Number planned: 15; Number enrolled: 15; Number analyzed: 13 for pharmacokinetics, 15 for safety.

Diagnosis and main criteria for inclusion: Healthy male or female volunteers, age 18 or older; Body mass Index between 20 and 30 and weighing between 50 and 90 kg; willing and able to sign the consent form; and for women of childbearing potential, a negative urine pregnancy test at screen and using a medically accepted contraceptive regimen.

Test product, dose and mode of administration, batch number: 3.9 mg/day Oxy TDS: 36 mg oxybutynin/system, batch # PD0001; Ditropan XL® Extended Release tablets, 10 mg/tablet, lot # 0101058, expires 12/2002.

Duration of treatment: Subject's received oxybutynin by transdermal administration for 7.5 days and oxybutynin by oral administration for 6 days with a 5 to 7 day between treatment interval for study drug

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washout and up to 21 days between the screening visit and start of the first treatment. The duration of a subjects total study participation could therefore be up to 42 days (screening visit to study exit).

Criteria for evaluation:

Primary variable: Pharmacokinetic variables C_{max}, C_{min}, AUC_{0-84}, T_{max}, and FI determined from plasma oxybutynin and DEO concentrations measured in serially collected blood samples 0, 84, 88, 92, 96, 102, 108, 112, 116, 120, 126, 132, 136, 140, 144, 150, 156, 160, 164, 168, 174, and 180 hours after application of the first transdermal system and at 0, 48, 52, 56, 60, 66, 72, 76, 80, 84, 90, 96, 100, 104, 108, 114, 120, 124, 128, 132, 138, and 144 hours after administration of the first Ditropan XL® tablet.

Secondary variables: Secondary variables included: 1) evaluation of the degree of oxybutynin metabolism with each route of administration, 2) salivary output measured 0, 12, 24, 36, 48, 60, 72, 84, and 96 hours after application of the second Oxy TDS and administration of the third Ditropan XL® tablet, and 3) adherence of the transdermal systems evaluated 84 hours after application of the first system and 24, 48, 72, and 96 hours after application of the second system.

Safety: Safety assessments included the monitoring of vital signs and adverse events.

Statistical Methods: Plasma concentration-time profiles for oxybutynin and DEO were characterized in terms of C_{max}, C_{min}, AUC_{0-84}, and T_{max}. C_{max}, C_{min}, and T_{max} were obtained by direct observation of the concentration-time curves. AUC_{0-84} was calculated using the trapezoidal method from time 0 to 84 hours after application of the second Oxy TDS and from time 0 to 84 hours after administration of the third Ditropan XL® tablet. Attainment of steady state was assessed by comparing the plasma oxybutynin concentrations at 84 hours after the 1st and 2nd Oxy TDS applications for the transdermal treatment using a paired t-test. Attainment of steady state for the Ditropan XL® treatment was assessed by comparing the plasma oxybutynin concentrations 24 hours after the second and sixth oral administrations using a paired t-test. The metabolism of oxybutynin between the treatments was assessed by comparing the ratios of AUC_{0-84} DEO to AUC_{0-84} oxybutynin using an analysis of variance (ANOVA) model appropriate for a 2x2 crossover design.

Descriptive statistics of system adhesion and adverse events were tabulated.

RESULTS: **Primary Variables:** Mean oxybutynin C_{max} and AUC_{0-84} values were 5% and 34% greater, respectively, with Oxy TDS administration compared to Ditropan XL®. This difference was greater for the active R-oxybutynin isomer, where the differences were 33% and 76% greater, respectively, between Oxy TDS and Ditropan XL®. Mean plasma oxybutynin concentrations reached steady-state concentrations during the first Oxy TDS application and were maintained during the wear period for the second system. Likewise, mean plasma oxybutynin concentrations reached steady-state concentrations following administration of the second Ditropan XL® Extended Release tablet and were maintained during the administration of an additional four tablets. Mean (± SD) racemic and R- and S-oxybutynin and DEO pharmacokinetic parameters are presented in the table below.

PK Parameter	Oxybutynin TDS		Ditropan XL®	
	R,S-Oxybutynin	R,S-DEO	R,S-Oxybutynin	R,S-DEO
C_{max} (ng/ml)	4.2 ± 1.0	4.9 ± 2.0	4.0 ± 1.5	15.2 ± 6.7
C_{min} (ng/ml)	2.1 ± 0.3	2.8 ± 1.1	1.3 ± 0.7	5.5 ± 4.1
AUC_{0-84} (ng•ml/hr)	259 ± 57	321 ± 114	194 ± 68	802 ± 369
T_{max} (median hrs)	28.1	28.1	52.1	48.1
FI	0.7 ± 0.2	0.5 ± 0.1	1.3 ± 0.5	1.1 ± 0.4

	R-Oxy	S-Oxy	R-DEO	S-DEO	R-Oxy	S-Oxy	R-DEO	S-DEO
C_{max} (ng/ml)	1.6±0.3	2.3±0.7	2.3±0.6	2.1±0.8	1.2±0.7	2.3±1.0	7.4±3.4	5.7±2.6
C_{min} (ng/ml)	0.8±0.2	1.1±0.1	1.4±0.5	1.2±0.4	0.4±0.2	0.8±0.5	2.9±2.6	2.5±1.8
AUC_{0-84} (ng•ml/hr)	104±17	144±31	162±45	146±52	59±30	117±52	399±237	334±173
T_{max} (median hrs)	21.1	21.1	21.1	36.1	60.1	30.1	10.1	6.1
FI	0.6±0.2	0.7±0.2	0.5±0.1	0.5±0.1	1.2±0.4	1.2±0.5	1.1±0.5	1.0±0.6

Secondary Variables: Significantly less ($p < 0.0001$) oxybutynin was metabolized to DEO following

transdermal delivery of oxybutynin compared to oral oxybutynin administration.

Significantly more saliva ($p = 0.0167$) was produced during transdermal oxybutynin administration than during the oral administration of oxybutynin. A significant negative correlation ($r = -0.5865$, $p = 0.0351$) was seen between increasing plasma DEO concentrations and lower saliva production. The correlation between plasma oxybutynin concentration and inhibition of saliva production was much less ($r = -0.3982$) and non-significant ($p = 0.1778$).

System adhesion was excellent with 95% of all transdermal systems being evaluated as > 90% adhered.

Safety Results: Six of 15 subjects experienced one or more adverse events at some time during the study, regardless of causality. Treatment-related adverse events were limited to one occurrence of nausea with Ditropan XL® treatment and one occurrence of skin rash with Oxy TDS treatment. All events were mild or moderate in severity. No unexpected or serious adverse events occurred. One subject was withdrawn from the study because of a non-study drug related adverse event.

DISCUSSION AND CONCLUSIONS: Application of the 3.9 mg/day Oxy TDS led to greater exposure to oxybutynin, the primary therapeutic moiety, compared to the 10 mg Ditropan XL®/day tablet. However, significant differences in DEO pharmacokinetics following Oxy TDS and oral administration were seen, where DEO $AUC_{0\text{-}84}$ and C_{max} values were 2.5 to 3 times greater with oral administration. Steady-state conditions were rapidly achieved with both delivery systems, being attained after application of the first Oxy TDS and after administration of the second Ditropan XL® tablet. Plasma oxybutynin concentrations with transdermal administration were less variable over time compared to Ditropan XL® administration. The transdermal administration of oxybutynin thus minimizes peak to trough fluctuations compared with those seen with once-a-day Ditropan XL® administration.

Greater saliva production during Oxy TDS application was observed suggesting that oxybutynin administration by the transdermal route may be associated with less dry mouth compared with oral administration. Paired comparisons of DEO and saliva revealed a significant negative correlation with Ditropan XL administration associated with greater plasma DEO concentrations and lower saliva production.

Oxy TDS exhibited excellent adherence, and was well tolerated. Administration of oxybutynin either by the transdermal or oral routes was not associated with any adverse trends in the evaluated safety parameters.

Date of the Report: 02 May 2002

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Reviewer's comment on the Study O01009
Overall the study conductance was acceptable from a pharmacokinetic perspective.

There were 2 withdrawals. Those are not related to the study medications.

It was noted that the C.V. % for desethyloxybutynin (DEO) QC 0.15 ng/ml appeared 43.73 %. This high C.V. is due to a single anomalous value. All other QC met acceptance criteria. This reviewer is of the opinion that this high variability due to one odd QC sample did not affect the data analysis and interpretation of the study results.

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/s/

Young-Moon Choi
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BIOPHARMACEUTICS

Ameeta Parekh
2/20/03 04:50:54 PM
BIOPHARMACEUTICS
I concur

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-351
Brand Name	Oxytrol ™
Drug Class	Anticholinergic
Drug Substance	Oxybutynin
Drug Product(s)	Oxybutynin trandermal system 3.9 mg
Dosing regimen	The recommended dose is one 3.9 mg/day system applied twice weekly (every 3-4 days)
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Sponsor	Watson Laboratories, Inc.
Type of submission	Original NDA (3S)
Date of submission	4/26/2001 9/4/2001 (BZ) 6/13/2001 (N000BB) 3/18/2002
Medical Division	HFD-580 (Division of reproductive and urologic drug products)
Reviewer	Young Moon Choi, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB division	OCPB/DPE-2 (HFD-870)

I. Executive Summary

Watson Laboratories, Inc. submitted NDA 21-351 for Oxytrol [TM], oxybutynin transdermal system (TDS) on 4/26/2001, seeking approval for TDS with oxybutynin delivery rates of [redacted] 3.9 mg/day for treatment of patients with overly active bladder with symptoms of urge urinary incontinence, urgency, and frequency.

In support of the present application, the sponsor conducted four pharmacokinetic studies (three single dose studies and one multiple dose study) and two clinical studies for efficacy and safety. The human pharmacokinetics and biopharmceuics section of the present NDA includes the results from the four PK studies as well as population PK data from two clinical trials. In addition to this information, *in vitro* skin permeation, drug release, and stability data were reported.

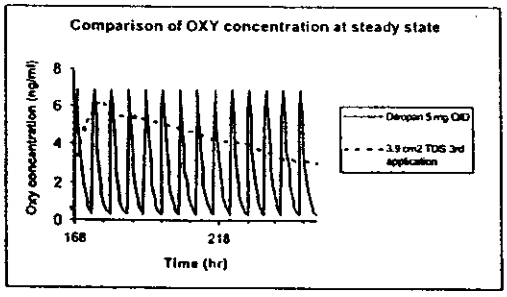
From a pharmacokinetic perspective, the clinical pharmacology and biopharmaceutics (CPB) data submitted in the human pharmacokinetics and biopharmaceutics section of the present NDA is acceptable. The sponsor adequately described the pharmacokinetics of oxybutynin (OXY), N-desoxybutynin (DEO; an active metabolite), and stereoisomers.

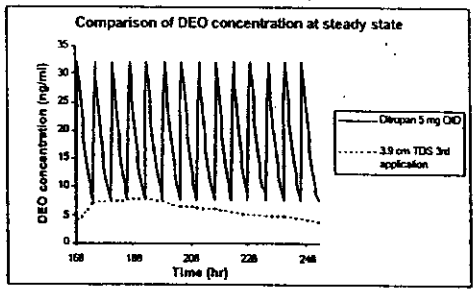
It should be noted that a response–exposure relationship of OXY or DEO after application of TDS was not explored. The sponsor was seeking an appropriate dose of TDS to maintain a comparable systemic exposure of OXY to that after administration of Ditropan 5 mg QID.

For OXY, a comparable Cmax (6.6 ng/ml vs 7.4 ng/ml) and larger AUC (408 vs. 224 ng.hr/min) were predicted following TDS 3.9 mg/day system every 96 hours compared to those following oral administration of 5 mg Ditropan QID (See the following figures: Left panel).

Of special concern is, however, the substantially less systemic exposure (4-6 times less) of DEO following the application of 3.9 mg/day TDS compared to Ditropan 5 mg (See the following figures: Right panel; Cmax 8.5 ng/ml vs. 41.0 ng/ml and AUC 561 vs 2528 ng.hr/min).

DEO is known to have equal pharmacological activity to OXY. Therefore, a poor efficacy as well as less adverse events, if any, may be due to the significantly less exposure to DEO.





Other important findings are:

- OXY 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.
- Systemic exposure to OXY following administration on abdomen is not significantly different from buttock, and hip.
- Steady state reached after second application of TDS. Steady state AUC and Cmax was 1.6 and 1.9 times higher than that after first application, respectively, indicating 60 and 90 % accumulation.
- The demographic characteristics, such as gender, age, and weight, appeared to not significantly affect pharmacokinetics of OXY and DEO following TDS application.
- In Phase I studies, during the wearing period of 84-96 hours, 19 out of 329 application did not appropriately adhere on the application site, i.e., more than 25 % of the active surface was detached. The patient information insert appeared to appropriately describe the treatment when the patch partially or completely falls off, i.e., press it back in place or apply a new patch in a different area. (See the proposed Patient Information Insert)
- The dissolution method and specifications are as follows:

Proposed parameters for the drug release methodology

Variable	Parameters
Apparatus Type	
Dissolution Medium	
Volume of Medium	
Temperature of Medium	
Speed of Rotation	
Sample Pull Times	
Sample Volume	
Units Tested	

Specification [Agency's recommendation (% label claim)]	
	Not less than

Note that the above method and specifications were accepted by the sponsor on 3/18/2002

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II completed the review of NDA 21-351. The clinical pharmacology and biopharmaceutics data in the human pharmacokinetics and biopharmaceutics section of the present NDA is acceptable. From a clinical pharmacology and biopharmaceutics perspective, some change in the labeling is recommended (refer to 'draft detailed labeling recommendation of this review' on page 33 of 100). The labeling, however, will be finalized at a later time, as appropriate.

II. Table of Contents

III. Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

Watson Laboratories, Inc. submitted NDA 21-351 for Oxytol ™, oxybutynin transdermal system (TDS), seeking approval for TDS with oxybutynin (OXY) delivery rates of — 3.9 mg/day for treatment of patients with overly active bladder with symptoms of urge urinary incontinence, urgency, and frequency.

The drug substance, OXY, is an anticholinergic agent. OXY is known to be well absorbed following oral administration, but undergoes extensive pre-systemic metabolism. The resulting oral bioavailability is less than 10% compared to intravenous dosing. N-desethyloxybutynin (DEO) is the primary circulating active metabolite and is present in plasma at concentrations approximately five times that of the parent compound. Both OXY and DEO undergo rapid metabolism and excretion, with half-lives of approximately 2 hours. The resulting large peak to trough concentration changes within the dosing interval and metabolic profile may contribute to the poor tolerability of the compound.

In this context, the sponsor expected that transdermal delivery offers several possible advantages over oral administration:

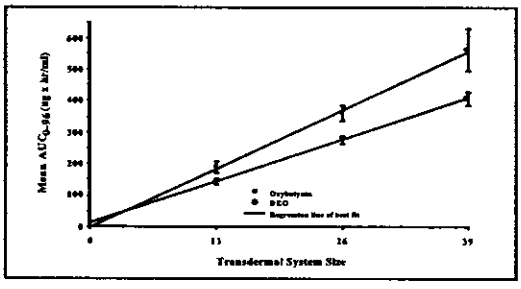
- The dosing interval is prolonged, leading to increased patient compliance and convenience.
- Pre-systemic metabolism may be avoided, leading to lower concentrations of the metabolite, which may improve tolerability.
- The continuous delivery of medication avoids the peaks that follow oral dosing that may also improve tolerability.

The sponsor conducted four pharmacokinetic (PK) studies (three single dose and one multiple dose for two weeks) and two clinical studies (one dose titration and one safety study).

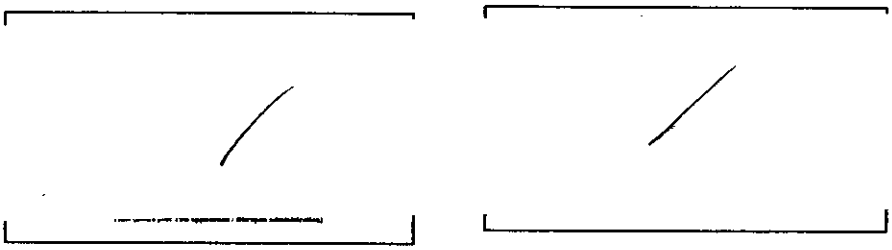
The human pharmacokinetics and biopharmaceutics section includes the results from the four PK studies as well as population PK data from two clinical trials. In addition to those information, *in vitro* skin permeation, drug release, and stability data were reported.

Based upon reviewing the data from a PK perspective, the important findings, potential issues, as well as reviewer's opinion on the management of those potential issues are summarized as follows:

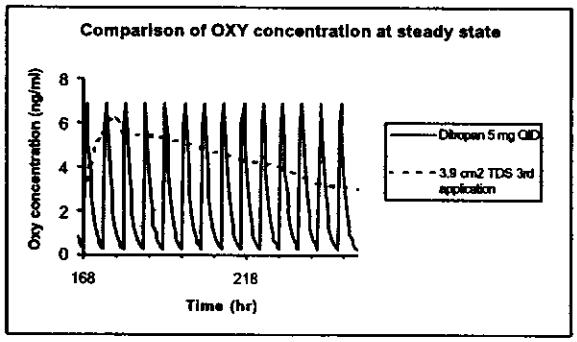
- The nominal oxybutynin transdermal delivery rate is 0.1 mg/cm^2 /day of active system surface area, resulting in nominal rates of 2.6 and 3.9 mg/day for the 26 and 39 cm^2 trasdermal delivery systems (TDS), respectively.
- The transdermal oxybutynin delivery is proportional to the active surface area of the applied TDS, increasing in a linear fashion with doses of 1.3, 2.6 and 3.9 mg/day. These results support to bridge the data obtained in the clinical trials using a multiple of 1.3 mg/day TDS or a combined 1.3 + 2.6 mg/day to the to-be-marketed formulation, i.e., 2.6 and 3.9/mg/day TDS.

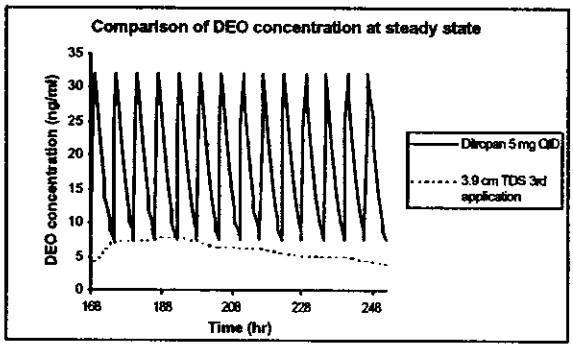


- There were substantial differences in systemic exposures of OXY and DEO after TDS application and those after oral administration of Ditropan 5 mg. The presence of low plasma concentrations of the primary active metabolite, N-desethyloxybutynin (DEO) during TDS application compared to oral administration of oxybutynin indicates less pre-systemic metabolism with transdermal delivery.



- Steady state AUC and Cmax was 1.6 and 1.9 times higher than that after first application, respectively, reflecting accumulation of 60 and 90 %, respectively.
- Based on the observed Cmins, the steady state was achieved after second TDS application.
- At steady state, similar Cmax (6.6 ng/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. However, the substantially less (8.5 vs 41.0 ng/ml for Cmax at steady state and 2528 vs 561 ng.hr/ml for AUCss) systemic exposure to DEO following TDS application is predicted (See the following figures). DEO is known to have equal pharmacological activity to OXY. Therefore, a poor efficacy as well as less adverse events, if any, may be due to the significantly less exposure to DEO.
- It was not successful to establish the exposure-response (PK/PD) relationship. Dose selection was not supported by PK-PD.





- Oxybutynin delivery following TDS applications to buttock and hip were bioequivalent compared TDS application to abdomen, which is the application site used in the pivotal Phase III clinical trial. While DEO exposure was 20 % higher after application on buttock compared to abdomen, this difference may not be a significant concern compared to the extreme DEO exposure after oral administration of Ditropan (See the following graph)

Oxybutynin and DEO pharmacokinetic parameters following application of a 39cm^2 Oxybutynin TDS to the abdomen, buttock, and hip (Protocol O99006).

	Oxybutynin			DEO		
Parameter (mean ± SD)	Abdomen	Buttocks	Hip	Abdomen	Buttocks	Hip
AUC_{0-120} (ng·ml/hr)	268 ± 93	303 ± 119	293 ± 111	389 ± 208	448 ± 240	436 ± 243
$AUC_{0-\infty}$ (ng·ml/hr)	284 ± 104	324 ± 136	311 ± 126	435 ± 259	504 ± 311	488 ± 301
C_{max} (ng/ml)	3.4 ± 1.1	4.0 ± 1.5	3.7 ± 1.3	5.0 ± 2.7	5.8 ± 2.9	5.7 ± 3.3
T_{max} (median hours)	36.0	48.0	48.0	48.0	48.0	48.0

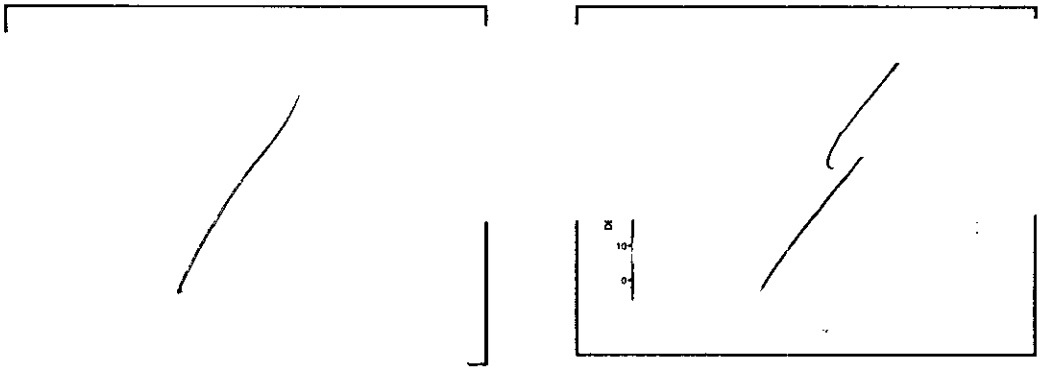
- After oral administration of racemate, systemic exposure to R-OXY was statistically significantly less than S-OXY, whereas the exposure to R-DEO was statistically significantly larger than S-DEO. This result may be due to the stereoselective metabolism of R-oxy by hepatic CYP 450 (CYP 3A4) assuming the absorption of R-and S-OXY are not different.
- After TDS application, the systemic exposures to both R-Oxy and R-DEO were lower than corresponding S-isomers. This contrasting result may be due to less hepatic first pass metabolism following TDS application than oral administration. Considering the degree of the difference, however, the clinical impact of this difference of the exposure of the stereo isomer is questionable.

R- and S-oxybutynin and DEO pharmacokinetic parameters following application of a single 39 cm^2 Oxybutynin TDS and oral administration of 5 mg oxybutynin chloride (Protocol O99005)

PK Parameter	Descriptive Statistic	R-Oxy	S-Oxy	R-DEO	S-DEO
39 cm^2 Oxybutynin TDS					
C_{max} ng/ml)	Mean ± SD Range	1.2 ± 0.3	1.6 ± 0.4	1.2 ± 0.5	1.4 ± 0.7
C_{avg} (ng/ml)	Mean ± S Range	0.8 ± 0.2	1.1 ± 0.3	0.8 ± 0.4	0.9 ± 0.5
AUC_{0-t} (ng·hr/ml)	Mean ± SD Range	85.8 ± 26.4	121.4 ± 34.0	83.9 ± 43.0	101.1±52.6
T_{max} (hours)	Median Mean ± SD Range	48.0 51.9 ± 30.5	48.0 54.9 ± 31.2	48.0 48.2 ± 26.7	48.0 50.6 ± 30.3
5 mg Oral Oxybutynin Chloride					
C_{max} ng/ml)	Mean ± SD Range	2.2 ± 1.7	4.1 ± 2.8	15.5 ± 3.7	10.9 ± 3.1
C_{avg} (ng/ml)	Mean ± SD Range	0.6 ± 0.5	0.9 ± 0.5	7.6 ± 2.8	5.3 ± .2.0
AUC_{0-t} (ng·hr/ml)	Mean ± SD Range	3.8 ± 3.1	5.5 ± 3.3	45.7 ± 17.1	31.8 ± 11.7
T_{max} (hours)	Median Mean ± SD Range	1.0 1.0 ± 0.4	0.8 0.8 ± 0.3	1.0 1.2 ± 0.6	1.0 1.0 ± 0.4

AUC 0-t: t=96 hours for TDS and t=6 hours for PO.

- There was considerable variability in systemic exposure, e.g., Cmax of OXY was in the range of [redacted] ng/ml after oral administration of 5 mg Ditropan (Δ) and [redacted] ng/ml after 3.9 mg/day TDS (○) This variability, however, appeared not associated with demographic characteristics with the Oxybutynin TDS. (See Pharmacometric Scientist's Review on page 96 of 100)



- The dissolution method and specifications are as follows:

Proposed parameters for the drug release methodology

Variable	Parameters
Apparatus Type	
Dissolution Medium	
Volume of Medium	
Temperature of Medium	
Speed of Rotation	
Sample Pull Times	
Sample Volume	
Units Tested	

Specification [Agency's recommendation (% label claim)]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	Not less than [redacted]

Note that the above method and specifications were accepted by the sponsor on 3/18/2002

Question Based Review

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General Attributes of the submission

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?
What is the proposed mechanism of drug action and therapeutic indications?
What is the proposed dosage and route of administration?

Oxybutynin (OXY) is a prescribed medication that is indicated for the relief of urinary symptoms of incontinence and urgency associated with detrusor instability.

The drug was first approved for use in the United States in July 1975. The recommended dose is oxybutynin chloride 5 mg, as tablet or syrup, administered 2 to 3 times daily.

Treatment is associated with a high incidence of anticholinergic adverse effects, particularly dry mouth, decreased sweating, and mydriasis with poor accommodation. For many patients, these side effects limit their ability to use the product effectively. Larger doses of oxybutynin, up to 40 mg/day, have been used in patients able to tolerate the associated anticholinergic effects, as well as alternate methods of administration, specifically, direct installation of oxybutynin solutions into the urinary bladder.

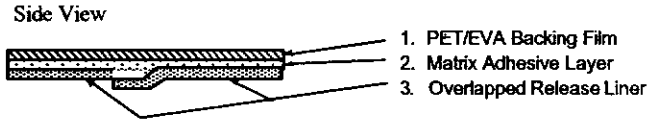
OXY is known to be well absorbed following oral administration, but undergoes extensive pre-systemic metabolism. The resulting oral bioavailability is less than 10% compared to intravenous dosing. N-desethyloxybutynin (DEO) is the primary circulating active metabolite and is present in plasma at concentrations approximately five times that of the parent compound. Both OXY and DEO undergo rapid metabolism and excretion, with half-lives of approximately 2 hours. The resulting large peak to trough concentration changes within the dosing interval and metabolic profile may contribute to the poor tolerability of the compound.

Watson Laboratories, Inc. is developed Oxytol ™, oxybutynin transdermal system (TDS), seeking for approval for TDS with oxybutynin delivery rates of 2.6mg/day and 3.9 mg/day for treatment of patients with overly active bladder with symptoms of urge urinary incontinence, urgency, and frequency. Oxybutynin TDS is an adhesive matrix transdermal system designed for the continuous administration of oxybutynin over a 3-4 day period (See following table for composition of the formulation).

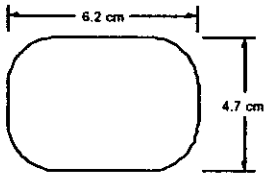
The sponsor expected that transdermal delivery offers several possible advantages over oral administration:

- The dosing interval is prolonged, leading to increased patient compliance and convenience.
- Pre-systemic metabolism may be avoided, leading to lower concentrations of the metabolite, which may improve tolerability.
- The continuous delivery of medication avoids the peaks that follow oral dosing that may also improve tolerability.

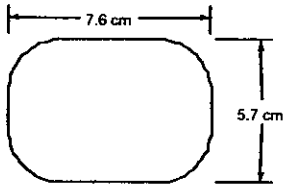
Diagram of the TDS system



Top View
26 cm^2 System Dimensions



39 cm^2 System Dimensions



Composition of the Oxybutynin TDS Matrix Adhesive Layer

The formulation of the adhesive laminate is the same for all systems, the composition of each patch is therefore proportional to the total surface area of the system. The nominal compositions of the 13, 26, and 39 cm^2 oxybutynin adhesive matrix systems used in pk/clinical studies are outlined in the following table. For comparison, then composition of the to-be-marketed formulation are summarized in the following table.

Nominal composition of the adhesive matrix for the oxybutynin transdermal systems used in PK studies

Component	13 cm^2 TDS		26 cm^2 TDS		39 cm^2 TDS	
	mg/system	% of matrix	mg/system	% of matrix	mg/system	% of matrix
Acrylic Adhesive						
Triacetin, USP						
Oxybutynin Base	12		24		36	
Total Weight of Adhesive Matrix						

Quantitative composition of the to-be-marketed Oxybutynin Trandermal Systems

Description of layers	Thickness	Mg/cm2		Mg/39 cm2 TDS
Backing film				
Oxybutynin				36.0
Triacetin, USP				
acrylic adhesive				
Release liner				
Total				

The sponsor conducted four pharmacokinetic studies (three single dose and one multiple dose for two weeks) and two clinical studies (Refer to the attached table of PK studies). Study 99003, a single dose study, in which an experimental formulation was used, was not reviewed. The other three PK studies, i.e., single dose, multiple dose, and site comparison, were thoroughly reviewed. All pharmacokinetic studies with Oxybutynin TDS were performed in healthy male and female volunteers.

General Clinical Pharmacology

What is the basis for selecting the response endpoints?
How are they measured in clinical pharmacolgy and clinical studies?
Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In a clinical trial, the primary efficacy endpoint was changes in the number of incontinent episodes recorded in urinary diary during a certain period (e.g. 7 days). The secondary endpoints were daily urinary frequency, urinary volume per void, quality of life scores, global assessment of disease state.

Two cytometric parameters, bladder volume to first detrusor contraction and the maximum bladder capacity, represent an objective assessment of bladder function. Both parameters are indicative of antimuscarinic activity resulting in reduced detrusor muscle tone and inhibition of detrusor contractions. In a dose-titration study, the above parameters were measured.

The sponsor adequately identified oxybutynin (OXY), N-desoxybutynin (DEO; an active metabolite), and stereoisomers after applying Oxytrol, a transdermal delivery system of oxybutynin (TDS) (See following section of Analytical section of the present review).

It was not successful, however, to establish PK-PD relationship. The dose selection was not supported by PK-PD relationship. The reasons for unsuccessful establishment for PK-PD relationship seemed to be due to the inappropriate design for such relationship and the considerable variation on PD response.

Without having information on concentration-effect relationship, the sponsor aimed to maintain a comparable OXY systemic exposure following application of TDS to that following Ditropan 5 mg QID, while to maintain the lower DEO exposure.

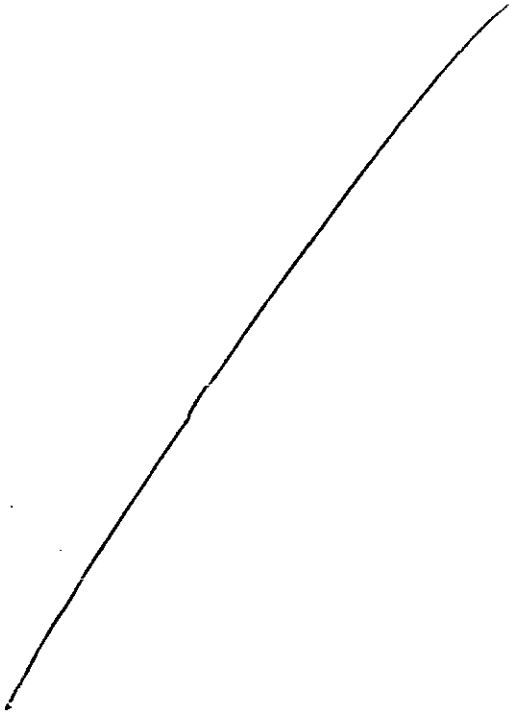
Therefore, the present review is focused on the comparative systemic exposures of OXY and DEO following administration of TDS to those after oral administration of Ditropan, an approved product.

It was noted that the sponsor provided only a single dose data for oral Ditropan administration. This reviewer, therefore, modeled the single dose data and simulated the systemic exposure profile after multiple oral administration to appropriately compare the systemic exposures after multiple application of TDS to those after oral administration.

Systemic exposure after Single dose

What is the plasma profile of oxybutynin and its active metabolte?
Is there any dose dumping?
Is there any difference in systemic exposure by differing the application site of TDS?

The relative bioavailability between oral and transdermal oxybutynin administration was assessed after single dose in Protocols O99005. The Oxybutynin TDS produced a gradual increase in plasma oxybutynin concentrations over 24 to 48 followed by sustained concentrations for the remainder of the 96 hour wear period (See the following graph).



Oxybutynin and DEO pharmacokinetic parameters following application of a 39 cm^2 Oxybutynin TDS and oral administration of a single 5 mg oxybutynin tablet (Protocol O99005)

PK Parameter	Descriptive Statistic	Oxybutynin TDS		Ditropan	
		Oxy	DEO	Oxy	DEO
C_{max} (ng/ml)	Mean ± SD SEM Range	3.0 ± 0.8 0.2	4.5 ± 1.8 0.4	7.4 ± 5.6 1.4	41.0±10.4 2.6
C_{max} (ng/ml) (0-96 hours)	Mean ± SD SEM Range	2.9 ± 0.9 0.2	4.4 ± 1.7 0.4	--	--
C_{avg} (ng/ml)	Mean ± SD SEM Range	2.2 ± 0.5 0.1	3.2 ± 1.3 0.3	2.2 ± 1.2 0.3	21.2 ± 7.3 1.8
AUC_{0-t} [a] (ng·hr/ml)	Mean ± SD SEM Range	235 ± 58 14.4	351 ± 140 35.1	13.2 ± 7.4 1.9	127 ± 44 10.9
$AUC_{0-\infty}$ (ng·hr/ml)	Mean ± SD SEM Range	245 ± 59 14.9	373 ± 159 39.7	14.0 ± 7.9 2.0	158 ± 71 17.8
T_{max} (hours)	Median Mean ± SD SEM Range	48.0 56.4 ± 34.9 8.7	48.0 57.2 ± 23.4 5.8	0.8 0.8 ± 0.3 0.1	1.0 1.0 ± 0.3 0.1
T_{max} (hours) (0-96 hours)	Median Mean ± SD SEM Range	48.0 45.8 ± 26.4 6.6	48.0 52.5 ± 18.0 4.5	--	--
$t_{1/2}$ (hours)	Mean ± SD SEM Range	7.2 ± 1.8 0.5	8.1 ± 2.7 0.7	1.3 ± 0.1 0.0	2.1 ± 0.6 0.2

[a] t represents 96 hours for TDS and 6 hours for Oxy.
Cavg estimated by AUC ÷ t .

Oxybutynin and DEO C_{max} was observed to occur in some subjects during the transient spike in plasma concentrations routinely seen after system removal and resulted in T_{max} values longer than the 96 hour system wear period. Recalculation of C_{max} and T_{max} values in these subjects over the 96 hour time of system application resulted in minimal change in C_{max}, but produced T_{max} mean values that more closely matched the median values.

Oxybutynin AUC during the application of a single 39 cm^2 Oxybutynin TDS for 96 hours was 18 times the AUC for 6 hours from a single 5 mg oxybutynin chloride tablet orally. However, Cmax following 39 TDS was half of 5 mg Ditropan. Furthermore, the Cmax of DEO appeared approximately 10 times less after single application.

It is more appropriate to compare the systemic exposures after chronic dosing than after single dose. Since no data was submitted for multiple dose of Ditropan, this reviewer conducted modeling of the plasma concentration data obtained from the study O99005 using WINNONLIN, a software, for both OXY and DEO. Then, simulated the plasma profile for OXY and DEO after multiple dose of Ditropan assuming linear pharmacokinetics. The simulated plasma concentration was compared to the plasma concentrations of OXY and DEO following TDS 3.9 (See the following section for resuts/graphical comparison).

While the sponsor stated that DEO is responsible for side effect, it is known that DEO has equal pharmacological activity. Therefore, the 6-7 fold less DEO exposure may be of concern from an efficacy perspective, if there is any lack of efficacy following application of TDS.

Systemic exposure after multiple dose

Does drug accumulate following chronic dosing?
Do the PK parameters change with time following chronic dosing?
Based on PK parameters, what is the degree of linearity or nonlinearity in the dose concentration relationship?

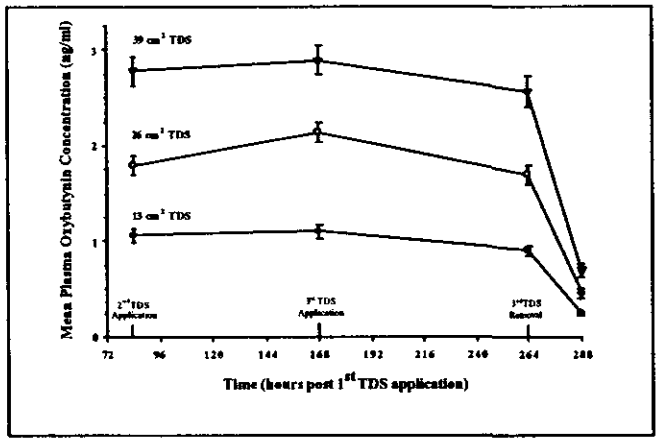
Multiple-dose pharmacokinetics for Oxybutynin TDS have been investigated in a Phase I pharmacokinetic study (Protocol O99007).

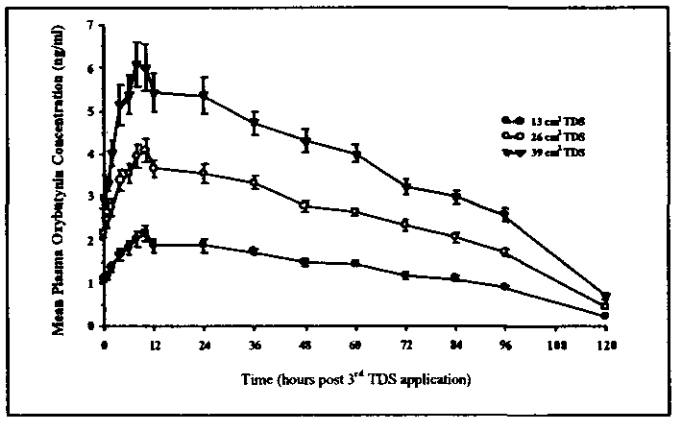
Protocol O99007 was a multiple-dose, 3-way crossover pharmacokinetic and bioavailability study to evaluate the 13, 26, and 39 cm^2 oxybutynin systems. All systems were applied three times sequentially to the abdomen for 84, 84, and 96 hours to normal volunteers.

Based on Cmin data, steady-state conditions were achieved following application of the second system (See following Figure upper panel).

Mean plasma oxybutynin concentrations for the three applications of each system size are illustrated in the following Figures. Serial plasma oxybutynin concentrations were obtained for pharmacokinetic analysis during application of the third Oxybutynin TDS (lower panel of the following figure).

Mean (± SEM) plasma oxybutynin concentrations following the sequential application of three 13, 26, and 39 cm^2 transdermal systems (Protocol O99007)





Oxybutynin TDS provided consistent oxybutynin delivery over the duration of their respective applications.

The three Cmin data indicates that the steady state was reached after second application of TDSA minimal accumulation (See the graph).

Based on the single dose data, minimal accumulation of OXY was expected. From a cross study comparison, steady staet AUC and Cmax was 1.6 and 1.9 times higher than that after first application, respectively.

Plasma oxybutynin concentrations declined steadily after removal of the last system.

Mean (± SEM) plasma DEO concentrations following the sequential application of three 13, 26, and 39 cm^2 transdermal systems (Protocol O99007)

Oxybutynin and DEO pharmacokinetics by TDS size (Protocol O99007)

PK Parameter	Descriptive Statistic	13 cm^2 System (N = 23)		26 cm^2 System (N = 23)		39 cm^2 System (N = 23)	
		OXY	DEO	OXY	DEO	OXY	DEO
C_{max} (ng/ml)	Mean ± SD	2.3 ± 0.8	2.7±1.3	4.4±1.3	5.3±1.7	6.6±2.4	8.5±5.4
	SEM	0.16	0.28	0.28	0.36	0.50	1.13
	Range						
C_{avg} (ng/ml)	Mean ± SD	1.5 ± 0.4	2.0±0.9	2.9±0.6	3.8±1.2	4.2±1.1	5.8±3.3
	SEM	0.09	0.18	0.13	0.26	0.23	0.70
	Range						
AUC_{0-96} (ng·hr/ml)	Mean ± SD	143±39	188±82	274±59	361±119	408±108	561±321
	SEM	8.21	17.02	12.39	24.86	22.45	66.87
	Range						
AUC_{0-96} (ng·hr/ml) (dose normalized)	Mean ± SD	429±118	564±245	410±89	542±179	408±108	561±321
	SEM	24.64	51.06	18.58	37.28	22.45	66.87
	Range						
T_{max} (hours)	Median	10.0	24.0	10.0	24.0	10.0	24.0
	Mean ± SD	20.3±16.4	22.7±16.9	13.6±9.5	19.6±11.7	17.9±18.2	20.4±17.9
	SEM	3.42	3.53	1.98	2.45	3.80	3.73
	Range						

Protocol O99009 was a multi-center, randomized, double-blind, placebo-controlled, Phase III, pivotal trial with an open-label, dose-titration extension in patients diagnosed with overactive bladder with symptoms of urge urinary incontinence and urinary frequency. Patients who met the eligibility criteria during screening and baseline evaluations were randomized to receive either active or placebo oxybutynin TDS. Three dose levels and placebo, administered using two system sizes (13 cm^2 and 26 cm^2 in combinations of placebo and active drug), were studied with patients assigned to a fixed dosing regimen during the double-blind period.

During the double-blind period, transdermal systems were applied twice a week to the abdomen for 12 weeks. Upon completion of the double-blind period, patients could enter a 12 week, open-label safety period. All patients were to begin the open-label period with the 13 cm^2 system and the dose titrated as required during the first four weeks. The dose remained fixed thereafter for the last eight weeks.

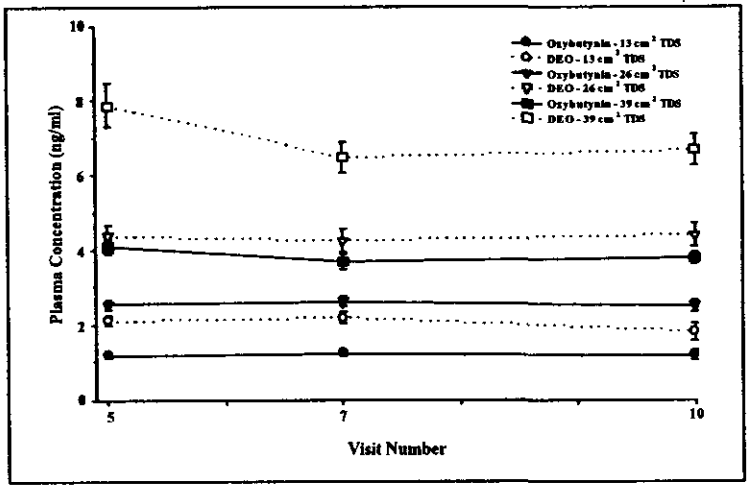
Systems used in this study were from 3 to 7 months of age at the time of their first use. Plasma oxybutynin concentrations were relatively constant over the 24 weeks of dosing. The plasma oxybutynin concentrations obtained after 24-48 hours following administration of 13 cm^2 TDS

system were approximately 2 and 3 times greater following application of the 26 and 39 cm^2 systems, respectively. However, this is only supportive data since the study was not appropriately designed for dose linearaity, i.e., blood sampling is irregular.

Summary of plasma oxybutynin and DEO concentrations (ng/ml) by treatment and visit (Protocol O99009)

	Oxybutynin			DEO		
	Visit 5	Visit 7	Visit 10	Visit 5	Visit 7	Visit 10
13 cm^2 Treatment Group						
N	115	104	33	114	104	33
Mean (SD)	1.18 (0.54)	1.24 (0.62)	1.17 (0.75)	2.10 (1.38)	2.19 (1.64)	1.83 (1.33)
Range						
%CV	46.2	49.8	64.2	65.7	74.9	72.9
26 cm^2 Treatment Group						
N	117	103	113	117	102	113
Mean (SD)	2.55 (1.42)	2.62 (1.38)	2.51 (1.54)	4.37 (3.21)	4.25 (2.95)	4.41 (3.37)
Range						
%CV	55.8	52.5	61.3	73.5	69.4	76.3
39 cm^2 Treatment Group						
N	110	100	180	110	100	180
Mean (SD)	4.08 (2.10)	3.69 (1.88)	3.80 (2.21)	7.88 (6.37)	6.47 (4.08)	6.67 (5.51)
Range						
%CV	51.6	51.1	58.2	80.8	63.0	82.6

Mean (± SEM) plasma oxybutynin and DEO concentrations by clinic visit and TDS size

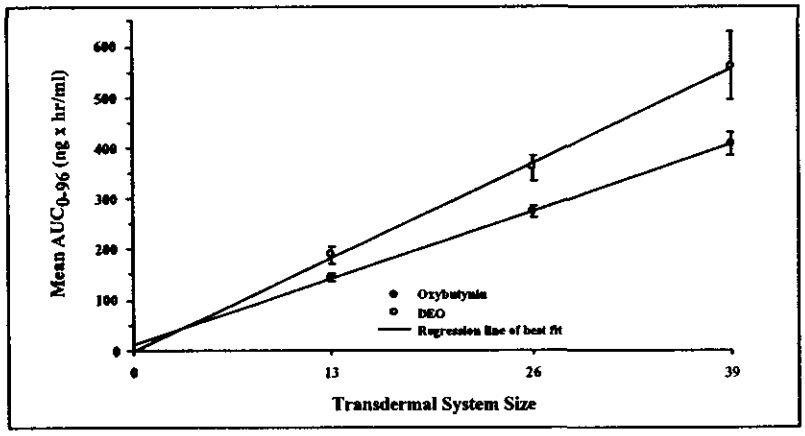


(Protocol O99009)

Dose-proportionality

Based on PK parameters, what is the degree of linearity or non-linearity in the dose-concentration relationship?

Dose proportionality was tested based on the results of O99007, a multiple, cross over study with the dose range of 13 to 39 cm ^{2} TDS. According to the results of the power model, oxybutynin appears to have dose linearity. The slope for oxybutynin AUC vs TDS are close to 1 (0.9521) and 95 confidence interval (0.8185 - 1.0859) includes slope 1. This data indicates that the OXY delivery is proportional to the active surface size. The data was also supportive to bridge the data obtained in the clinical trials in which multiple of 13 and 26 cm2 TDS was used to to-be-marketed 39 cm2 TDS.



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What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and /or clinical safety and efficacy data support the approval of the to-be-marketed product?

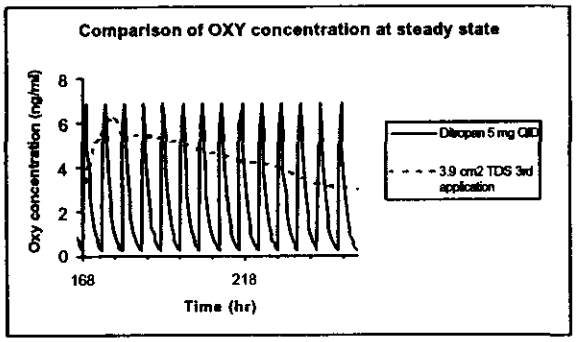
In the pivotal clinical trial, the sponsor evaluated the safety/efficacy of simultaneous 13+26 patches in lieu of a single 39 patches, and wish to market a single 39 patch. Based on the dose-linearity 13, 26, and 39 TDS (O99007) and the comparable plasma levels of oxybutynin and DEO following administration of 13 + 26 (double blind portion of trial) vs. 39 (open label extensions of trial) (O99009) is supportive that the simultaneous application of a 13 + 26 system results in similar plasma concentrations of OXY and DEO following application of 39 system.

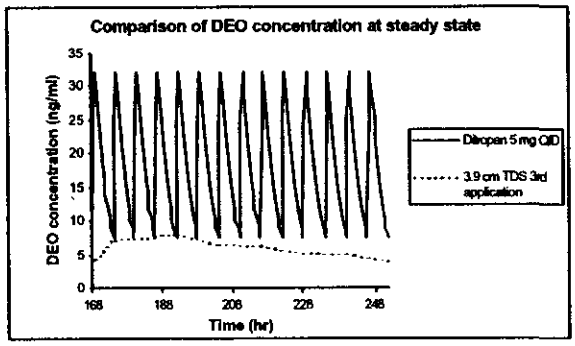
Comparison of systemic exposure of OXY and DEO after multiple dose

How are the systemic exposure of OXY and DEO compared ?

It was noted that the sponsor provided only a single dose data for oral Ditropan administration. This reviewer modeled the single dose data and simulated the systemic exposure profile after multiple oral administration, and compared the systemic exposures after multiple application of TDS to those after oral administration.

At steady state, similar Cmax (6.6 ng/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. However, the substantially less (8.5 vs 41.0 ng/ml for Cmax at steady state and 2528 vs 561 ng.hr/ml for AUCss) systemic exposure to DEO following TDS application is predicted (See the following figures).





DEO is known to have equal pharmacological activity to OXY. Therefore, a poor efficacy as well as less adverse events, if any, may be due to the significantly less exposure to DEO.

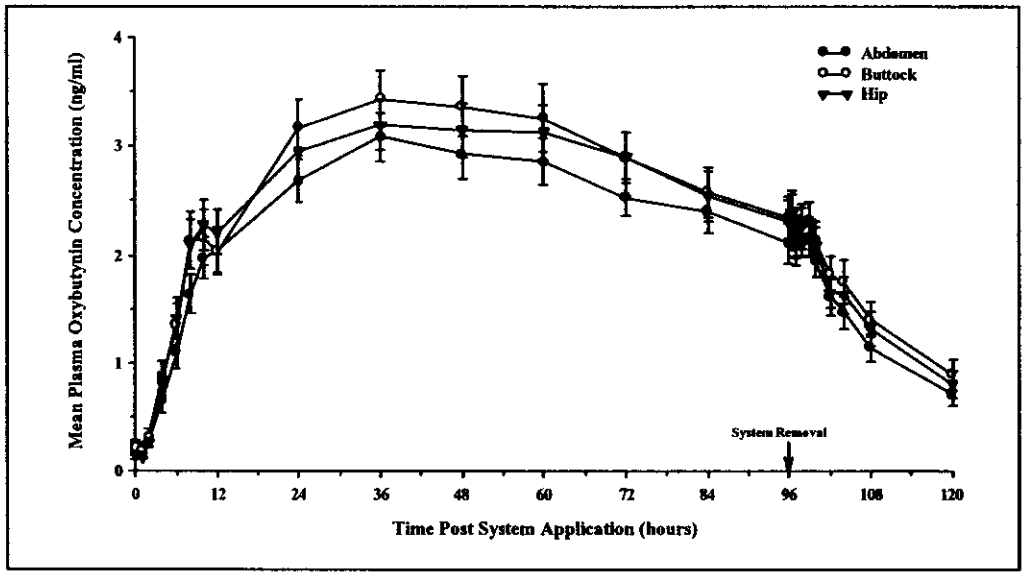
Does the application site affect the systemic exposure ?

Bioavailability/bioequivalence at different application sites

Study O99006 evaluated the relative bioavailability of oxybutynin following the 96 hour application of a 39 cm^2 OXY TDS to the abdomen, buttock, and hip in 24 normal male and female volunteers. The abdomen was selected as the reference site.

Plasma OXY concentration-time curves following system application to the abdomen, buttock, and hip were similar in shape but somewhat different in magnitude between the 3 application sites. Plasma oxybutynin concentrations were slightly higher following system application to the buttock, followed by the hip, and finally the abdomen. The mean plasma oxybutynin concentration profiles following system application to the abdomen, buttock, and hip were roughly parallel to each other indicating comparable time-dependency. The mean plasma oxybutynin concentrations following the single 39 cm^2 Oxybutynin TDS application to the abdomen, buttock, and hip are illustrated in the following Figure.

Mean (± SEM) plasma oxybutynin concentrations following application of a 39 cm^2 Oxybutynin TDS to the abdomen, buttock, and hip (Protocol O99006).



The resulting oxybutynin pharmacokinetic parameters are shown in Table. Residual oxybutynin from prior treatments was observed at hour 0 of treatment periods 2 and 3. $AUC_{0-\infty}$ values were therefore accordingly adjusted to account for this carryover. This is acceptable. Adjusted $AUC_{0-\infty}$ values for treatment periods 2 and 3 were calculated by subtracting the fraction $C_{0(\text{current period})}/k_{el}$ from the $AUC_{0-\infty}$ values, where C_0 = the plasma concentration at hour 0 for the current treatment period and k_{el} = the elimination rate constant.

Oxybutynin and DEO pharmacokinetic parameters following application of a 39cm^2 Oxybutynin TDS to the abdomen, buttock, and hip (Protocol O99006).

	Oxybutynin			DEO		
Parameter (mean ± SD)	Abdomen	Buttocks	Hip	Abdomen	Buttocks	Hip
AUC_{0-120} (ng·ml/hr)	268 ± 93	303 ± 119	293 ± 111	389 ± 208	448 ± 240	436 ± 243
$AUC_{0-\infty}$ (ng·ml/hr)	284 ± 104	324 ± 136	311 ± 126	435 ± 259	504 ± 311	488 ± 301
$AUC_{0-\infty}$ (ng·ml/hr) (adjusted)	279 ± 99	319 ± 128	308 ± 126	423 ± 239	491 ± 284	481 ± 293
C_{max} (ng/ml)	3.4 ± 1.1	4.0 ± 1.5	3.7 ± 1.3	5.0 ± 2.7	5.8 ± 2.9	5.7 ± 3.3
T_{max} (median hours)	36.0	48.0	48.0	48.0	48.0	48.0

The buttock and the hip application sites were determined for oxybutynin to be 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 exposure was about 20 % higher after application of TDS in buttock than abdomen. 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.

Relative oxybutynin and DEO bioavailability following application of a 39 cm^2 Oxybutynin TDS to the abdomen, buttock, and hip (Protocol O99006).

		Buttock:Abdomen		Hip:Abdomen	
Parameter		Ratio	90% CI	Ratio	90% CI
Oxybutynin	C_{max}	1.1519	1.0668, 1.2439	1.0802	1.0005, 1.1661
	$AUC_{0-\infty}$,	1.1361	1.0641, 1.2129	1.0891	1.0203, 1.1625
	$AUC_{0-\infty}$ (adjusted)	1.1428	1.0696, 1.2210	1.0954	1.0255, 1.1702
DEO	C_{max}	1.2033	1.0885, 1.3301	1.1257	1.0186, 1.2440
	$AUC_{0-\infty}$,	1.1657	1.0765, 1.2623	1.1097	1.0250, 1.2014
	$AUC_{0-\infty}$ (adjusted)	1.1751	1.0843, 1.2735	1.1189	1.0327, 1.2124

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How does the stereoselective metabolism impact on the systemic exposure of OXY and DEO after TDS application?

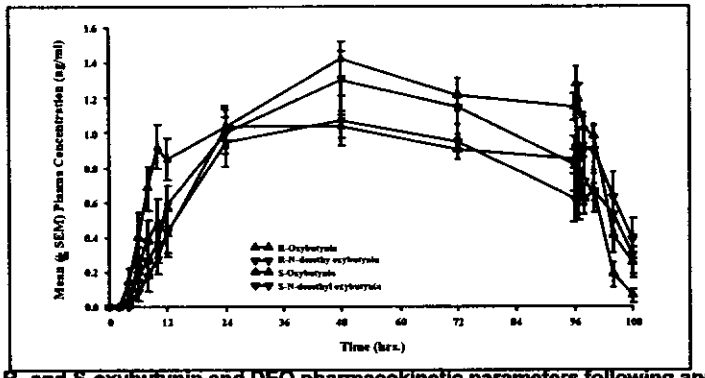
It is important to investigate the systemic exposure of stereoisomers of OXY and DEO due to the known stereo selective hepatic metabolism as well as stereo selective pharmacological activity.

Following oral administration of oxybutynin, the mean plasma R-oxybutynin C_{max} and AUC_{0-t} were significantly lower ($p < 0.0001$) than the S-oxybutynin C_{max} and AUC_{0-t}, whereas mean R-DEO C_{max} and AUC_{0-t} were significantly ($p < 0.0001$) greater than S-DEO C_{max} and AUC_{0-t}.

Following TDS application, the mean plasma concentrations of R-oxybutynin and R-DEO were approximately equal. The mean plasma R-oxybutynin C_{max} and AUC_{0-t} were both significantly lower ($p < 0.0001$) than the mean plasma S-oxybutynin C_{max} and AUC_{0-t}. Mean plasma R-DEO C_{max} and AUC_{0-t} were non-significantly lower ($p = 0.0899$ and 0.0607, respectively) than the mean S-DEO C_{max} and AUC_{0-t}.

This contrasting results may be due to less first pass metabolism following TDS application than oral administration. However, the clinical impact of this difference of the exposure of the stereo isomer is questionable due to the significantly larger production of R-DEO, which has equal pharmacologycal activity as R-OXY, after oral administration.

Mean (± SEM) plasma R- and S-oxybutynin and -DEO concentrations following application of a 39 cm^2 TDS (Protocol O99005).



R- and S-oxybutynin and DEO pharmacokinetic parameters following application of a single 39 cm^2 Oxybutynin TDS and oral administration of 5 mg oxybutynin chloride (Protocol O99005)

PK Parameter	Descriptive Statistic	R-Oxy	S-Oxy	R-DEO	S-DEO
39 cm^2 Oxybutynin TDS					
C_{max} ng/ml)	Mean ± SD Range	1.2 ± 0.3	1.6 ± 0.4	1.2 ± 0.5	1.4 ± 0.7
C_{avg} (ng/ml)	Mean ± S Range	0.8 ± 0.2	1.1 ± 0.3	0.8 ± 0.4	0.9 ± 0.5
AUC_{0-t} (ng·hr/ml)	Mean ± SD Range	85.8 ± 26.4	121.4 ± 34.0	83.9 ± 43.0	101.1±52.6
T_{max} (hours)	Median Mean ± SD Range	48.0 51.9 ± 30.5	48.0 54.9 ± 31.2	48.0 48.2 ± 26.7	48.0 50.6 ± 30.3
5 mg Oral Oxybutynin Chloride					
C_{max} ng/ml)	Mean ± SD Range	2.2 ± 1.7	4.1 ± 2.8	15.5 ± 3.7	10.9 ± 3.1
C_{avg} (ng/ml)	Mean ± SD Range	0.6 ± 0.5	0.9 ± 0.5	7.6 ± 2.8	5.3 ± .2.0
AUC_{0-t} (ng·hr/ml)	Mean ± SD Range	3.8 ± 3.1	5.5 ± 3.3	45.7 ± 17.1	31.8 ± 11.7
T_{max} (hours)	Median Mean ± SD Range	1.0 1.0 ± 0.4	0.8 0.8 ± 0.3	1.0 1.2 ± 0.6	1.0 1.0 ± 0.4

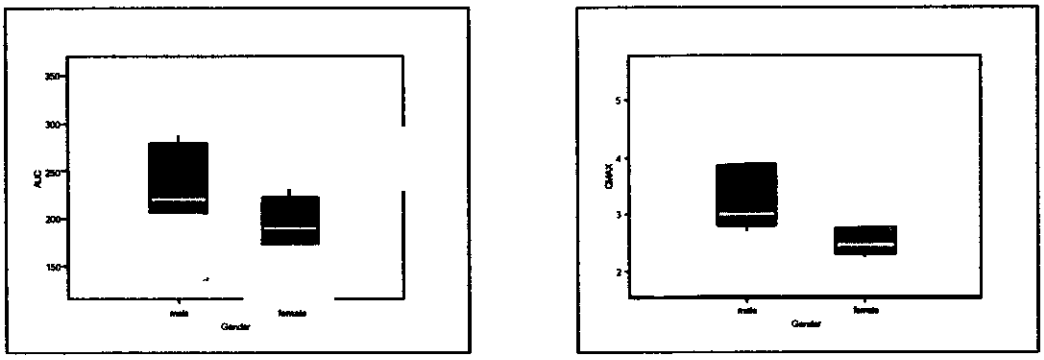
Gender Effect

Is there any difference in systemic exposures of OXY and DEO in male and female?
If there is any difference, is a significant clinical impact expected?

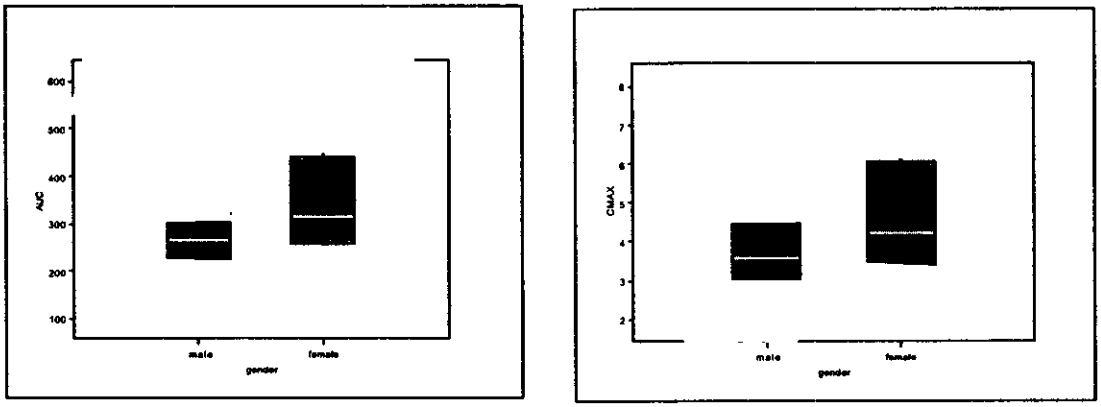
There were discrepancies between studies in the results.
In site-to-site bioavailability studies, both OXY and DEO exposures were higher in females, while a single dose and a multiple dose studies, OXY exposure was higher in male and DEO exposure was higher in females.

Considering (1) the variability, (2) the magnitude of the difference, (3) the observed discrepancy from study to study, (4) similar pharmacological activity of DEO as OXY, and (4) no gender effect indicated by population analysis from a clinical trial, the clinical impact of the gender effect on PK is considered not significant (See the following figures, table and Pharmacometrics review in attachment).

Study O99005: OXY exposure comparison (AUC Left panel; Cmax Right panel); n=8 for each gender



Study O99005: DEO exposure (AUC left panel; Cmax Right panel) : n=8 for each gender.



Following the single application of a 39 cm^2 Oxybutynin TDS in Protocol O99005 to the abdomen for 96 hours, mean oxybutynin C_{max} and $AUC_{0-\infty}$ values were approximately 21% and 14% higher, respectively, in males than in females. However, mean DEO C_{max} and $AUC_{0-\infty}$ values were 18%

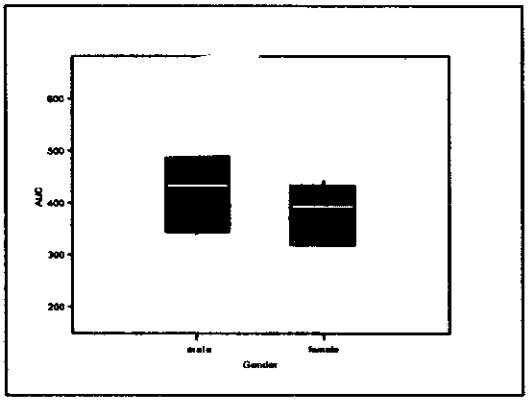
and 22% higher in the females. Average DEO:oxybutynin $AUC_{0-\infty}$ ratios were 33% higher in females than in males.

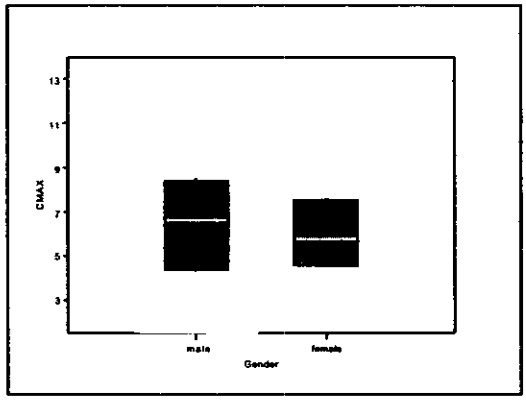
Oxybutynin and DEO pharmacokinetic parameters by gender following application of a 39 cm^2 Oxybutynin TDS (Protocol O99005)

PK Parameter	Descriptive Statistic	Oxybutynin		DEO	
		Male	Female	Male	Female
C_{max} (ng/ml)	Mean ± SD SEM Range	3.4 ± 1.0 0.4	2.7 ± 0.5 0.2	4.0 ± 1.8 0.6	4.9 ± 1.8 0.6
AUC_{0-108} (ng·hr/ml)	Mean ± SD SEM Range	255 ± 66 23.4	214 ± 42 14.9	312 ± 136 48.2	390 ± 142 50.2
$AUC_{0-\infty}$ (ng·hr/ml)	Mean ± SD SEM Range	263 ± 68 23.9	226 ± 48 16.8	327 ± 151 53.2	420 ± 163 57.5
T_{max} (hours) (overall)	Median Mean ± SD SEM Range	24.0 39.1 ± 25.6 9.1	96.5 73.8 ± 35.6 12.6	48.0 45.0 ± 15.4 5.4	60.0 69.4 ± 24.4 8.6
T_{max} (hours) (0-96 hrs)	Median Mean ± SD SEM Range	24.0 33.0 ± 12.4 4.4	60.0 58.5 ± 31.1 11.0	48.0 45.0 ± 15.4 5.4	48.0 60.0 ± 18.1 6.4
$t_{1/2}$ (hours)	Mean ± SD SEM Range	6.4 ± 1.2 0.4	8.1 ± 2.1 0.7	7.3 ± 2.8 1.0	8.9 ± 2.6 0.9
DEO:Oxy $AUC_{0-\infty}$ Ratio	Mean ± SD SEM Range	1.2 ± 0.4 0.13	1.8 ± 0.4 0.16	--	--

A similar pattern for OXY C_{max} and AUC was observed following repeated application of 39 cm^2 TDS values 12-36% higher in males than in females (Protocol O99007).

Study O99007; OXY exposure (AUC left panel; Cmax right panel); n=11 for male; n=12 for female





However, following application of 39 cm^2 systems to the abdomen, buttock, and hip, mean oxybutynin C_{max} values were approximately 6, 19, and 31%, respectively, higher in females than in males (Protocol O99006) though mean DEO C_{max} values were still 36 - 68% higher in females than in males.

In vivo adhesion

Is there any detachment of the TDS from the application site during the suggested wearing duration?

Because of the long duration of application of TDS, i.e., 3-4 days of application on the skin, it is important to ensure that the TDS is not detached during the wearing period.

The number of partial and complete transdermal system detachments for Oxybutynin TDS were reported in six studies (O96003, O96017, O99005, O99006, O99007, O99009). System adhesion was verified during each of these six studies by observation of the application site by study site personnel at each study visit. System adhesion was rated as good to excellent in all studies in which adhesion was evaluated.

The adhesion of Oxybutynin TDS as reported in the four pharmacokinetic, the one efficacy, and the one safety and efficacy trial are summarized in the following table.

Adhesion of Oxybutynin TDS

Protocol #	# of Subjects	Total # of System Applications	# of Good to Excellent Attachments[a]	# of Partial Detachments[b]	# of Complete Detachments
Phase I Studies					
O96003	16	15	15	0	0
O99005	18	17	17	0	0
O99006	24	72	71	1	0
O99007	26	225	207	17	1
Phase II / III Studies					
O96017	76	225	219	3	3
O99009[c]	515	3755	3712	21	25

[a] Good to excellent attachment includes an adhesion range of greater than or equal to 75% of the surface area of the system being applied to the skin.

[b] Partial detachment includes an adhesion range of less than 75% of the system surface area of the system being applied to the skin but not complete detachment from the skin.

[c] System applications during the double-blind portion of the study only.

Adhesion scores of ≥ 75% represent good to excellent adhesion and would be expected to be associated with appropriate transdermal delivery of oxybutynin. Adhesion assessments of < 74% may be associated with lower amounts of delivered drug or with individuals unable to appropriately use the transdermal system. Of the 329 Oxybutynin TDS applied during the 4 Phase I pharmacokinetic studies, 1 (0.3%) became completely detached, and 17 (5%) became partially detached. Thus, the adherence of 95% (311/329) of the Oxybutynin TDS applications in these four pharmacokinetic studies were rated as ≥ 75% adhered to the skin and would be expected to perform as anticipated.

Adhesion was only periodically evaluated during the Phase II and III studies. Of the 3980 Oxybutynin TDS applications in the Phase II and III trials, 25 (0.6%) were observed at clinic visits to have became completely detached and 24 (0.6%) became partially detached during routine clinical use. Similar to the pharmacokinetic studies, > 98% of the systems applied in the Phase II and III studies were assessed as being ≥ 75% attached and thus would be expected to perform as anticipated.

This reviewer is of the opinion that the adhesion performance is acceptable and the patient information insert appeared to appropriately described the treatment when the patch partially or completely fall off, i.e., press it back in place or apply a new patch in a different area. (See the proposed Patient Information Insert)

Delivery rate following application of TDS

What was the delivery rate of oxybutynin following application of TDS?

Because relatively large amount of OXY (36 mg) is loaded in a 3.9 mg/day system, it is of importance to investigate the delivery rate and ensure no dose-dumping that may results in sudden high systemic exposure.

The sponsor investigated the delivery rate based on the residual contents of OXY after application of TDS as follows:
Residual oxybutynin content was measured in worn systems in the pharmacokinetic studies. System depletion data were not obtained in the Phase II and III studies.

The estimated amount of oxybutynin delivered was calculated as the differnece between the analyzed residual content of the used systems and the mean value of the unused control system.

Based on data from the residual content analysis of the used systems (n=291; Studies O99005, O99006 and O99007), the nominal oxybutynin delivery rate was 0.10 ± 0.02mg/cm^2 system surface area/24 hours (refer to the attachment of the present review for detailed method of estimation of the delivery rate).

This reviewer is of the opinion that the delivery rate estimation is acceptable considering the relatively steadily maintained plasma concentration without any evidence of dose-dumping (See the plasma profile figures after single dose and multile dose from Study O99005, 99006 and 99007)

Dissolution

The drug release test method for oxybutynin followed the USP method for transdermal systems.

Proposed test method parameters are as follows:

Proposed parameters for the drug release methodology

Variable	Parameters
Apparatus Type	
Dissolution Medium	
Volume of Medium	
Temperature of Medium	
Speed of Rotation	
Sample Pull Times	
Sample Volume	
Units Tested	

The proposed drug release specifications for Oxybutynin TDS at — , are as follows:

Proposed drug release specifications for Oxybutynin TDS by the sponsor

	Specification (% Label Claim) Level 1	Specification (% Label Claim) Level 2	Specification (% Label Claim) Level 3
Oxybutynin			
Oxybutynin			
Oxybutynin			

Drug release specifications for oxybutynin were established using data for — , of Oxybutynin TDS. The mean ± SD of the oxybutynin assay data at batch release and on stability for systems stored at 25°C/60%RH corresponded to 98 ± 2 % of the label claim. The data were within the proposed product specifications of the label claim — , for oxybutynin.

The results of drug release testing for the Oxybutynin TDS used in the pharmacokinetic studies and the efficacy and safety trials are as follows:

Oxybutynin TDS drug release data from pharmacokinetic and clinical study batches

Protocol Number	Code/Control Number	Nominal Oxybutynin Delivery Rate (mg/day)	Oxybutynin Release Average % Label Claim (range of individual values)		
O96003	0063-1/95Z174	1.4	58	87	101
O96017	0140-0/97Z002	1.3	47	71	94
O99005	0352-0/99Z137	3.9	43	75	96
O99006	0352-0/99Z137	3.9	43	75	96
O99007	0350-0/00Z133	1.3	37	67	90
	0351-0/99Z143	2.6	43	75	97
	0352-0/99Z137	3.9	43	75	96
O99009	0350-0/99Z173	1.3	42	76	93
	0351-0/99Z178	2.6	44	79	95
	0351-0/99Z162	2.6	43	76	96
	0352-0/99Z183	3.9	44	76	96
	0352-0/99Z167	3.9	45	79	98

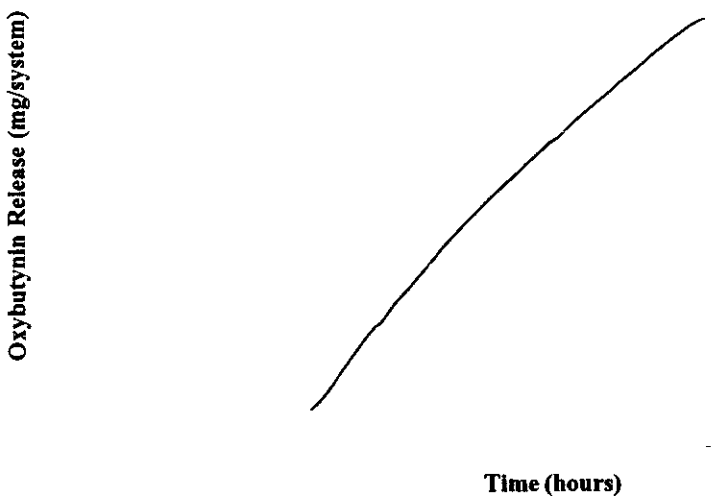
Oxybutynin release was rapid with more than — of the total system content delivered in vitro within approximately — The release profiles measured at — for 39 cm^2 systems stored under standard temperature (25°C) and humidity (60%) conditions were

virtually identical to those measured at zero time, indicating that system performance remained consistent over this storage interval . Additionally, no decrease in oxybutynin and triacetin content was observed during — , storage period.

Data for 13 cm^2 and 26 cm^2 systems are available for storage duration's up to — respectively. Release profiles for these 13 and 26 cm^2 systems were indistinguishable from the 39 cm^2 system profiles under comparable storage conditions and times.

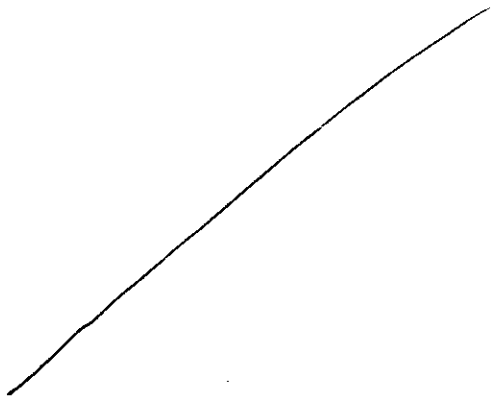
As seen with the 39 cm^2 systems , no decrease in oxybutynin and triacetin content was observed during the — . storage periods. The conclusions reached for the — data thus apply equally to the data over — supporting a proposed shelf-life of at least 2 years for this product.

In vitro oxybutynin release profiles for 39 cm^2 Oxybutynin TDS after 0, 13, 26, 39, and 52 weeks storage at 25°C and 60% relative humidity (system control number 99Z137)



Oxybutynin TDS oxybutynin and triacetin content over time under storage conditions of 25°C and 60% relative humidity

Protocol(s)	Control Number	System Size	Time (weeks in storage)	Oxybutynin Content (mg/system)	Triacetin Content (mg/system)
O96017	97Z002	13			
O99007 O99009	99Z143	26			
O99005 O99006 O99007	99Z137	39			



Reviewer's comment on the dissolution specification:

The sponsor agreed the agency's following dissolution specifications (Refer to the letter from the sponsor dated 3/18/2002).

	Agency's recommendation % label claim	Sponsor's proposal % label claim
	Not less than	Not less than

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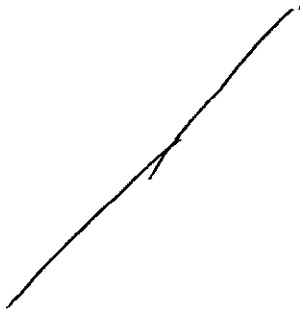
Analytical Methodology

Plasma samples were analyzed for racemic oxybutynin and DEO concentrations by , using high performance liquid chromatography (HPLC) with mass spectrometric (MS) detection. Plasma R- and S-oxybutynin and R- and S-DEO concentrations were analyzed by by HPLC

Determination of Plasma Racemic Oxybutynin and DEOConcentrations



Identification of oxybutynin, DEO, and both internal standards was based on their retention times and the detector response to their selected specific ions. For retention time determination, a mixture consisting of oxybutynin, DEO, and both internal standards was injected at the beginning, middle, and end of each analytical run.

A set of nine oxybutynin and DEO calibration standards , were analyzed with every series of analytical assays. The peak area for oxybutynin and DEO, and their respective internal standards were determined for each calibration standard and the peak area ratios between oxybutynin/oxybutynin-D5 and DEO/DEO-D5 were calculated using linear regression (1/concentration weighting) describing the calibration curve. This method was validated with minimum quantifiable plasma oxybutynin and DEO concentrations of 50 pg/ml using a plasma sample volume of for oxybutynin in Protocol O99009).

Determination of Plasma R- and S-Oxybutynin and DEO Concentrations

Clinical study and quality control plasma R- and S-oxybutynin and R- and S-DEO concentrations were calculated by interpolating the peak area ratios from the corresponding standard curve using linear regression with 1/concentration weighting. Each analytical batch consisted of up to 84 clinical study plasma samples, six quality control samples (2 sets of

with the quality control samples regularly distributed throughout the clinical samples. The method was validated to minimum quantifiable plasma R- and S-oxybutynin and R- and S-DEO concentrations of , using a plasma sample volume of .

***In vivo* analytical methods summary**

Study No.	Type of Biological Fluid	Analytical Method[a]	Sensitivity/Range[a] (ng/ml)	Specificity
O96017	Plasma	LC-MS		NSI[b]
O99005	Plasma	LC-MS (racemic) LC-MS/MS (enantiomers)		NSI[b]
O99006	Plasma	LC-MS		NSI[b]
O99007	Plasma	LC-MS		NSI[b]
O99009	Plasma	LC-MS		NSI[b]

[a] For both oxybutynin and DEO

[b] No significant interference (NSI) at the retention times of oxybutynin, DEO or internal standards were observed from contaminants or endogenous compounds in blank human plasma samples.

Detailed labeling recommendation (Draft)

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_____ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

5 § 552(b)(5) Draft Labeling

Appendices

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Assessment of Total Drug Delivery

Residual oxybutynin content was measured in worn systems in the pharmacokinetic studies. System depletion data were not obtained in the Phase II and III studies. Based on data from the residual content analysis of the used systems, the nominal oxybutynin delivery rate was calculated to be 0.10 mg/cm^2 system surface area/24 hours.TDS Collection Methods

Immediately after application of a transdermal system, the protective liner covering the adhesive side of the system was returned to its original pouch.

Following use, the systems were removed from the subject's skin, applied to an over-sized siliconized release liner, and placed into a protective pouch. For each subject, the pouch containing the release liner, the pouch containing the used system, and a matching randomly selected unopened control system were shipped and maintained frozen until analysis. In that way, control systems experienced similar environmental conditions in the clinic and during transit for determination of study drug content.

Analytical Method for Oxybutynin Content of Used Systems

All used and control 10, 13, 26, and 39 cm^2 systems were analyzed in the same laboratory using the same methodology. The system and release liner were weighed to 0.1 mg. The release liner was then peeled from the system, separately weighed, and then discarded. The remaining system was added to a 60 ml bottle containing 50 ml of HPLC grade acetonitrile, taking care that the system didn't adhere to the sides or bottom of the bottle, and the oxybutynin from each system extracted by mechanically shaking for 24 hours. Quantitation of oxybutynin in the acetonitrile extracts was accomplished by . The method was validated and has been shown to have adequate accuracy, precision, and reproducibility. Used and control systems from all Phase I studies were analyzed according to the method indicated in the following table.

Methods for residual oxybutynin drug content estimation in 10, 13, 26, and 39 cm^2 Oxybutynin TDS used in 4 phase I studies

Protocol Number	Nominal Oxybutynin System Content/Daily Delivery Rate (mg)	System Size (cm^2)	General Method	Product-Specific Method
O96003	1.4	10		
O99005	3.9	39		
O99006	3.9	39		
O99007	1.3	13		
	2.6	26		
	3.9	39		

Results of Oxybutynin Content in Used Systems

Depletion of oxybutynin from the systems used in the pharmacokinetic studies was determined from analysis of the oxybutynin contained in the control systems and the residual oxybutynin contained in the used systems. The estimated amount of oxybutynin delivered was calculated as the difference between the analyzed residual content of the used systems and the mean value of the unused control systems. The mean oxybutynin depletion data are shown for the four Phase I studies in Table.

Table Oxybutynin depletion from Oxybutynin TDS and nominal delivery rates

Protocol Number	No. of systems analyzed	System Size (cm^2)	Control Number	Oxybutynin Depletion Mean (SD) (mg/day)	Oxybutynin Depletion Mean (SD) ($mg/day/cm^2$)	% of Oxybutynin Content Delivered from the TDS/Application Period Mean (SD)	Nominal Oxybutynin Delivery Rates (mg/day)
O96003	12	10	95Z174	1.38 (0.2)	0.14 (0.02)	42.4 (6.1)	1.4
O99005	16	39	99Z137	2.99 (0.5)	0.08 (0.01)	33.3 (5.5)	3.9
O99006	72	39	99Z137	3.56 (0.7)[a]	0.09 (0.02)[a]	39.5 (7.3)[a]	3.9
O99007	72	13	99Z133	1.51 (0.3)[b]	0.12 (0.03)[b]	46.1 (10.8)[b]	1.3
	71	26	99Z143	2.83 (0.5)[b]	0.11 (0.02)[b]	43.1 (7.8)[b]	2.6
	72	39	99Z137	3.96 (0.8)[b]	0.10 (0.02)[b]	40.3 (8.2)[b]	3.9
Overall[c]	303	–	–	–	0.10 (0.02)	41.8 (9.0)	–

[a] represents the overall average daily depletion of the systems applied to the abdomen, buttock, and hip over a 96 hour application time frame.

[b] represents the overall average daily depletion for the three sequentially applied systems over an 11 day time frame

[c] data from the 10 cm^2 systems used in Protocol O96003 (control number 95Z174) are not included in the overall calculations.

Determination of the Nominal Oxybutynin Delivery Rate

The nominal oxybutynin delivery rate was calculated from residual content analysis data as mg of oxybutynin delivered per cm^2 of system surface area per 24 hours for the 13, 26, and 39 cm^2 systems. The 10 cm^2 system used in Protocol O96003 was produced from a different formulation than that used in the definitive Phase I studies and in the Phase II and Phase III studies. Data from these systems was therefore not used in the calculation of the nominal delivery rate. The overall oxybutynin delivery rate of 0.10 ± 0.02 $mg/cm^2/day$ was then multiplied by the surface area of each system size to yield a nominal oxybutynin delivery rate of 1.3, 2.6, and 3.9 mg/day for the 13, 26, and 39 cm^2 systems, respectively.

Table of all pharmacokinetic and bioavailability studies

Report #/ Start Date-Status	NDA Location of Report/ Tabulation/ CRF	Principal Investigator/ Country	Study Design[a]	Treatment Group	Study Drug[b]/ Nominal Delivery Rate (mg/day)/ System Size (oral dose; mg/day)	Control No./ Site of Manufacturer[b]/ Date	# Enrolled/ # Completed	Age Mean (SD) Range	Race (%) White/Black/ Other	Duration of Drug Treatment
Phase I – Bioavailability/Pharmacokinetic Studies										
O96003 6/10/96 - Completed			O SD COW R	All Groups Oxy TDS Oxy tablet	 Oxy/1.4/10 cm^2 Oxy/NAP/5 mg	 95Z174/WLU/11/95 K33750/NA/NA	15/15 (15 completed; only PK data for 1st 12 completers analyzed)	31 (7) 20-42	92/8/0	 4 days 1 day
O99005 11/3/99 – Completed			O COW R SD	All Groups Oxy TDS Oxy tablet	 Oxy/3.9/39 cm^2 Oxy/NAP/5 mg	 99Z137;WLU/ 9/99 98078828/NA/NA	18/16	32.6 (7.4) 19 - 45	100/0/0	 4 days 1 day
O99006 2/8/00 – Completed			O COW R MD	All Groups Oxy Abdomen Oxy Buttock Oxy Hip	 Oxy/3.9/39 cm^2 Oxy/3.9/39 cm^2 Oxy/3.9/39 cm^2	 99Z137/WLU/ 9/99 99Z137;WLU; 9/99 99Z137;WLU; 9/99	24/24	48.9 (17.7) 19 – 76	92/0/8	 4 days 4 days 4 days
O99007 2/6/00 – Completed			O COW R MD	All Groups Oxy – 13 cm^2 Oxy – 26 cm^2 Oxy – 39 cm^2	 Oxy/1.3/13 cm^2 Oxy/2.6/26 cm^2 Oxy/3.9/39 cm^2	 99Z133/WLU/ 9/99 99Z143/WLU/ 9/99 99Z137/WLU/ 9/99	26/24	32.8 (13.0) 19 - 65	58/38/4	 10 days 10 days 10 days

[a]Cont = continuous, COW = crossover with intervening washout period(s), DB = double-blind, DD – double dummy, DT = dose titration, F = fixed dose, MC = multi-center, MD = multiple dose, NA = not available, NAP = not applicable, O = open label, PG = parallel group, R = randomized, SD = single dose, Seq = sequential, WLU = Watson laboratories, Salt Lake City, Utah, USA

[b]Placebo capsules were prepared by Watson Laboratories, Utah under cGMP conditions and were identical in appearance to the active capsules.

Phase II – Safety/Efficacy Study										
O96017 10/6/97 – Completed			DB DD R MC DT MD PG	All Groups			76/74	63.3 (14.1) 27 – 85	95/5/0	
				Placebo	Placebo/NAP/ 13 cm^2	96Z203/WLU/ 12/96				6 weeks
				Oxy TDS	Oxy/1.3/13 cm^2	97Z002/WLU/ 1/97 [b]				6 weeks
				Placebo capsule	Placebo/NAP/ 0 mg	98056601/NA/NA				6 weeks
				Oxy tablet	Oxy/NAP/10-22.5 mg					6 weeks

[a]Cont = continuous, COW = crossover with intervening washout period(s), DB = double-blind, DD – double dummy, DT = dose titration, F = fixed dose, MC = multi-center, MD = multiple dose, NA = not available, NAP = not applicable, O = open label, PG = parallel group, R = randomized, SD = single dose, Seq = sequential, WLU = Watson laboratories, Salt Lake City, Utah, USA

[b]Placebo capsules were prepared by Watson Laboratories, Utah under cGMP conditions and were identical in appearance to the active capsules.

Phase III – Urge Urinary Incontinence Study										
O99009 1/18/00 – Completed			DB R MC DD MD PG	All Groups			520/447	61.4 (13.3) 20 – 88	91; 6; 3	
				Placebo	Plac/NAP/13cm^2 Plac/NAP/26cm^2	99Z125/WLU/ 8/99 99Z115/WLU/ 8/99				12 weeks
				Oxy 13 cm^2 Cont	Oxy/1.3/13 cm^2	99Z173/WLU/11/99				
				Oxy 26 cm^2 Cont	Oxy/2.6/26 cm^2	99Z162/WLU/10/99 99Z178/WLU/11/99				
			O DT MD	Oxy 13, 26, 39 cm^2 Seq	Oxy/1.3/13 cm^2 Oxy/2.6/26 cm^2	99Z173/WLU/11/99 99Z162/WLU/10/99 99Z178/WLU/11/99				4 weeks
					Oxy/3.9;/39 cm^2	99Z167/WLU/11/99 99Z183/WLU/11/99				
			O F MD	Oxy 13, 26, 39 cm^2 Cont	Oxy/1.3/13 cm^2 Oxy/2.6/26 cm^2	99Z173/WLU/11/99 99Z162/WLU/10/99 99Z178/WLU/11/99				8 weeks
					Oxy/3.9/39 cm	99Z167/WLU/11/99 99Z183/WLU/11/99				

[a]Cont = continuous, COW = crossover with intervening washout period(s), DB = double-blind, DD – double dummy, DT = dose titration, F = fixed dose, MC = multi-center, MD = multiple dose, NA = not available, NAP = not applicable, O = open label, PG = parallel group, Plac = placebo, R = randomized, SD = single dose, Seq = sequential, WLU = Watson laboratories, Salt Lake City, Utah, USA

[b]Placebo capsules were prepared by Watson Laboratories, Utah under cGMP conditions and were identical in appearance to the active capsules.

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32 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

___✓___ § 552(b)(5) Draft Labeling

Summary of Individual study

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Individual study
Study O9005

Name of Sponsor/Company: Watson Laboratories, Inc - Utah., Salt Lake City, Utah 84108	**Location of Full Report in the Submission**	*(For National Authority Use only)*
Name of Finished Product: Oxybutynin transdermal system	**Volume:**	
Name of Active Ingredient(s): Oxybutynin	**Page:**	

Title of Study: Single-Dose Pharmacokinetics Of Oxybutynin Following Oral And Transdermal Administration In Healthy Volunteers

Investigators: —

Study Center(s): —

Studied period (years): 1999 **(date of first enrollment):** 03-NOV-99 **(date of last completed):** 16-NOV-99	**Phase of development:** Phase I

Objectives: The primary objective of this study was to evaluate and compare the pharmacokinetics and metabolism of oxybutynin (both racemic and individual enantiomers) administered as a single 39 cm^2 transdermal system applied to the abdomen and as a single orally administered 5 mg Ditropan® tablet. Secondary objectives were to assess the local skin tolerability and the adhesion of the transdermal system over a 96 hour wear period, and to compare bioanalytical results for plasma oxybutynin and DEO concentrations as determined by two analytical laboratories.

Methodology: This was a randomized, open-label, two-way crossover study. The subjects were assigned to receive the two study treatments (Treatments A and B) in randomized sequence (A/B or B/A) with each subject receiving each study treatment once. Blood samples were collected for analysis of plasma racemic and enantiomeric oxybutynin and DEO concentrations over 108 hours after application of the oxybutynin transdermal system (oxybutynin TDS) and over 6 hours after Ditropan administration.

The treatment phase consisted of two study periods (Periods I and II). In each study period, subjects were administered either one 5 mg Ditropan tablet or wore the oxybutynin TDS for 96 hours during which blood samples were collected for assay of plasma oxybutynin and DEO concentrations. When assigned to wear the transdermal system, subjects were confined for two 12-hour intervals (Day 1 and Day 4) to allow for frequent phlebotomy during these intervals. At other phlebotomy time-points on Days 2-3, the subjects returned to the study site as outpatients. When taking the Ditropan tablet, subjects were confined for 6 hours to allow for frequent phlebotomy. The start of the two study periods were separated by 7 days. The duration of the entire study (excluding the screening visit) was 2 weeks for each subject.

Number of patients (planned and analyzed): Number planned: 12; Number enrolled: 18, Number analyzed: 16 for pharmacokinetics, 18 for safety.

Diagnosis and main criteria for inclusion: Healthy males and females, age 18 or older; Body Mass Index > 20 and < 28 and weight ≥ 50 and ≤ 90 kg; and willing and able to sign the consent form.

Test product, dose and mode of administration, batch number: 39 cm^2 Oxybutynin TDS, control # 99Z137; 5 mg Ditropan tablet, lot # 98078828 (exp. 9/2002).

Duration of treatment: Oxybutynin TDS treatment – 96 hours; Ditropan treatment – single administration

Criteria for Evaluation:

Primary variables: The pharmacokinetic variables AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and T_{max} for racemic oxybutynin, DEO, and their enantiomers were calculated from their respective plasma concentrations measured in serially collected blood samples. Collection times were as follows: 0 (within 30 minutes prior to application of the oxybutynin transdermal system), 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 96.5, 97, 98, 100, 104, and 108 hours following system application and 0 (within 30 minutes prior to tablet administration), 10, 20, 30, 45, 60, 90, 120, 180, 240, and 360 minutes after Ditropan administration.

Secondary variables: Total oxybutynin delivery from the systems over 96 hours was estimated from the difference in measured oxybutynin content of used systems and mean content of control systems and from $AUC_{0-\infty}$ values. Local skin tolerability was evaluated one and 12 hours after system removal. Adherence of the systems to the skin was evaluated 12 hours after system application and thereafter on a daily basis until system removal.

Safety: Safety assessments included pre- and post-treatment physical examinations, pre- and post-study clinical laboratory tests, and adverse events. Each adverse event was evaluated for duration, intensity, and relationship to the test articles.

Statistical Methods: Descriptive statistics and graphic displays were prepared for the pharmacokinetic parameters. Descriptive statistics of system adhesion and safety data, including assessment of application site skin tolerability and adverse events, were tabulated.

RESULTS

Primary Variables: Mean (± SD) pharmacokinetic parameters based on racemic and individual enantiomer plasma concentrations are presented in the tables below.

	Oxybutynin TDS		Ditropan	
PK Parameter	Oxybutynin	DEO	Oxybutynin	DEO
AUC_{0-t} (ng•hr/ml)	235 ± 58	351 ± 140	13 ± 7	127 ± 44
$AUC_{0-\infty}$ (ng•hr/ml)	245 ± 59	373 ± 159	14 ± 8	158 ± 71
C_{max} (ng/ml)	3.0 ± 0.8	4.5 ± 1.8	7.4 ± 5.6	41.0± 10.4
T_{max} (median hrs)	48.0	48.0	0.8	1.0

	Oxybutynin TDS				Ditropan			
PK Parameter	Oxybutynin		DEO		Oxybutynin		DEO	
(mean ± SD)	R	S	R	S	R	S	R	S
AUC_{0-t} (ng•hr/ml)	85.8 ± 26.4	121.4 ± 34.0	83.9 ± 43.0	101.1±52.6	3.8 ± 3.1	5.5 ± 3.3	45.7 ± 17.1	31.8±11.7
$AUC_{0-\infty}$ (ng•hr/ml)	-	-	-	-	3.8 ± 3.1	5.5 ± 3.3	62.3 ±3 0.8	42.2 ± 19.4
C_{max} (ng/ml)	1.2 ± 0.3	1.6 ± 0.4	1.2 ± 0.5	1.4 ± 0.7	2.2 ± 1.7	4.1 ± 2.8	15.5 ± 3.7	10.9 ± 3.1
T_{max} (median hrs)	48.0	48.0	48.0	48.0	1.0	0.8	1.0	1.0

Secondary Variables: Residual analysis of the used systems indicated that the oxybutynin systems delivered 12 ± 0.05 mg (mean ± SEM) oxybutynin/96 hours. When estimated using $AUC_{0-\infty}$ values, the oxybutynin systems delivered 8.3 ± 0.5 mg oxybutynin/96 hours.

Both R-oxybutynin and R-DEO AUC values were lower than AUC values for S-oxybutynin and S-DEO following oxybutynin TDS application. The pattern was different following oral administration where the AUC value for R-

oxybutynin was lower than the value for S-oxybutynin but higher for R-DEO than for S-DEO.

System adherence was good for all systems with greater than 80% of all evaluations graded as 4 (> 90% of system surface area adhered).

Skin tolerability was good to excellent with a majority of all evaluations indicating either no erythema or mild erythema immediately after system removal. No severe erythema was observed and no subjects complained of other skin-associated problems.

Safety Results: When all adverse events, regardless of causality, were considered, 56% (10/18) of the subjects experienced one or more adverse events. When all treatment-related adverse events were considered, 44% (8/18) of the subjects experienced one of more adverse events. The most frequently reported adverse events (> 10%), regardless of causality, were dizziness in 2 (12%), headache in 2 (12%), and nausea in 2 (12%) subjects following Ditropan administration and headache in 6 (33%), nausea in 3 (17%), and vomiting in 2 (11%) subjects following oxybutynin TDS application. All events resolved without sequelae.

Two subjects were withdrawn early from the study. One subject requested withdrawal after receiving oxybutynin TDS but before receiving Ditropan because of a family emergency. This withdrawal was not study related. The second subject was withdrawn during study period 2 after receiving oxybutynin TDS because of adverse events (headache, nausea, and vomiting) considered by the investigator to be related to the study medication.

Discussion and Conclusions:

The oxybutynin TDS provided consistent delivery over the 4-day application period and was well tolerated. Significant differences in pharmacokinetics are apparent between oral and transdermal administration, supporting the potential for equal efficacy and lower side effects with TDS treatment.

The TDS delivered oxybutynin consistently over the 4-day application period, supporting the proposed twice-weekly dosing regimen. The delivery profile was consistent with a skin depot effect, indicated by the short lag time following TDS application, a transient spike in plasma concentration following removal of the matrix system, and a somewhat prolonged apparent elimination half-life. Plasma DEO concentrations followed a similar pattern, with average concentrations about 50% greater that those of the parent compound. The plasma concentrations profile and pharmacokinetic parameters following oral administration were consistent with previous literature reports.

The delivery rate, and total dose, from the oxybutynin TDS were estimated by two methods. analysis of residual drug content of used transdermal systems and measured AUC and a standard, literature derived clearance value. Residual analysis indicated a delivery rate of 3 mg/day, or 12 mg over the 4-day application period, a value consistent with prior cumulative in vitro skin flux experiments.

The 39 cm^2 TDS is anticipated to be the largest system required for therapeutic use and should therefore approximate the upper range of required dosing. Plasma concentration comparisons between TDS and oral dosing for the parent compound and active R-isomer support this projected dosing requirement. Similar comparisons may be made to indicate the potential tolerability of TDS compared to oral treatment and are consistent with comparison for DEO and the R-DEO isomer regarding the potential for anticholinergic side effects.

The extensive first-pass metabolism of oral oxybutynin indicated a preferential metabolism of the R-isomer of oxybutynin. This trend was also reflected in the mean plasma concentrations during TDS administration in that R-oxybutynin were lower than S-oxybutynin. This stereo-selective metabolic effect may also contribute to the reduction in anticholinergic side-effects that have been observed during transdermal treatment.

Although there were differences between genders in the pharmacokinetic parameters in the current study, the small number of subjects, and relatively large variability preclude any conclusions to be drawn from the current data.

The oxybutynin matrix transdermal system exhibited good adherence, was well tolerated and was not associated with any adverse trends in the evaluated safety parameters.

Study O99006

Name of Sponsor/Company: Watson Laboratories, Inc. - Utah, Salt Lake City, Utah 84108	**Location of Full Report in the Submission**	***(For National Authority Use only)***
Name of Finished Product: Oxybutynin matrix transdermal system	**Volume:**	
Name of Active Ingredient(s): Oxybutynin	**Page:**	

Title of Study: Single-Dose Pharmacokinetics Of Oxybutynin Following Transdermal Administration To The Abdomen, Buttocks, And Hip In Healthy Volunteers

Investigators: —

Study Center(s): —

Studied period:

IRB Approval: 10 January 2000
First subject, first visit: 08 February 2000
Last subject, last visit: 18 March 2000

Phase of development: Phase I

Objectives: The primary objectives of this study were (a) to evaluate and compare the pharmacokinetics and metabolism of oxybutynin administered as a single 39cm^2 transdermal system to different areas of the body and (b) to determine the bioequivalence of a buttock and hip application site to an abdominal application site. Secondary objectives were to assess (a) the local skin tolerability and (b) the adhesion of the transdermal system over a 96 hour wear period.

Methodology: This was a randomized, open-label, three-way crossover study. Subjects were assigned to receive the three study treatments (Treatments A, B, and C) in randomized sequence with each subject receiving each study treatment once. Blood samples were collected for analysis of oxybutynin and N-desethyloxybutynin (DEO) concentrations during the 120 hours after application of each system.
The treatment phase consisted of three study periods (Periods I, II, and III). In each study period, subjects wore the study system on either the abdomen (Treatment A), buttocks (Treatment B), or hip (Treatment C) for 96 hours as outpatients. After application of each study system, subjects were confined for one 12-hour interval (Day 1 morning to evening) and for one 24 hour interval (Day 4 morning to Day 5 morning) to allow for frequent phlebotomy during these intervals. At other phlebotomy time-points on Days 1-3, the subjects returned to the study site as outpatients. The start of each study period was separated by 7 days.

Number of patients (planned and analyzed): Number planned: 24; Number enrolled: 24; Number analyzed 24

Diagnosis and main criteria for inclusion: Healthy males and females, age 18 or older; Body Mass Index ≥ 20 and ≤ 28 and weight ≥ 50 and ≤ 90 kg; willing and able to sign the consent form.

Test product, dose and mode of administration, batch number: 39 cm^2 oxybutynin transdermal system, control number 99Z137.

Duration of treatment: 3 weeks overall (96 hours per system application)

Criteria for Evaluation:

Primary variables: The pharmacokinetic variables $AUC_{0\text{-}120}$, $AUC_{0\text{-}\infty}$, adjusted $AUC_{0\text{-}\infty}$, C_{max}, and T_{max} for oxybutynin and DEO were calculated from plasma concentrations of oxybutynin and DEO measured in serially collected blood samples 0 (within 30 minutes prior to each system application), 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 96.5, 97, 98, 99, 100, 102, 104, 108, and 120 hours following application of each system.

Secondary variables: Total oxybutynin delivery from the systems when applied for 96 hours was estimated

from the difference in measured oxybutynin content of used systems and mean content of control systems and from $AUC_{0-\infty}$ values. Local skin tolerability was evaluated one and 24 hours after system removal. Adherence of the systems to the skin was evaluated 1, 2, 4, 6, 8, 10, and 12 hours after application, and on a daily basis thereafter.

Safety: Safety assessments included pre- and post-treatment physical examinations, pre-study clinical laboratory tests, and tracking of adverse events. Each adverse event was evaluated for duration, intensity, and its relationship or association to the test articles.

Statistical Methods: The primary pharmacokinetic end-points were oxybutynin and DEO AUC_{0-120}, $AUC_{0-\infty}$, adjusted $AUC_{0-\infty}$, C_{max}, and T_{max} for each study system, the estimated oxybutynin delivery based on system depletion analysis and AUC_{0-120} values, and the bioequivalence of the abdominal application site compared to the buttock and hip application sites.

Plasma concentration-time profiles for oxybutynin and DEO were characterized in terms of AUC_{0-120}, $AUC_{0-\infty}$, C_{max}, and T_{max}. C_{max}, and T_{max} were obtained from direct observation of the concentration-time curves. AUC was calculated using the trapezoidal method from time 0 to 120 hours and from time 0 to infinity with the average elimination rate constant of the systems from all three application sites used in the $AUC_{0-\infty}$ calculations. Bioequivalence of the three application sites was determined by evaluating the test:reference ratio of C_{max} and $AUC_{0-\infty}$ for oxybutynin and DEO using an ANOVA model appropriate for a three period crossover design. The abdominal site was the reference site. Non-parametric Wilcoxon paired signed rank tests were conducted to compare T_{max}. For subjects with non-zero plasma oxybutynin and DEO concentrations at hour 0 for treatment periods 2 and 3, $AUC_{0-\infty}$ was adjusted by subtracting the amount C_o/k_{el}.

Descriptive statistics of system adhesion and safety data, including assessment of application site skin tolerability and adverse events, were tabulated.

RESULTS:

Primary Variables: Mean plasma oxybutynin and DEO plasma concentrations gradually increased over approximately 36 hours, reaching a relatively stable level for approximately 24 hours before declining slightly over the remaining duration of the system application period. The characteristic lag time before the appearance of plasma drug concentrations was observed after initial system application. A transient increase in plasma oxybutynin and DEO concentrations were seen 30 minutes after system removal which then steadily declined. All three application sites exhibited the same concentration-time course pattern. Pharmacokinetic parameters based on plasma oxybutynin and DEO concentrations are presented in the table below.

Parameter	Abdomen		Buttocks		Hip	
(mean ± SD)	Oxybutynin	DEO	Oxybutynin	DEO	Oxybutynin	DEO
AUC_{0-120} (ng•ml/hr)	268 ± 93	389 ± 208	303 ± 119	448 ± 240	293 ± 111	436 ± 243
$AUC_{0-\infty}$ (ng•ml/hr)	284 ± 104	435 ± 259	324 ± 136	504 ± 311	311 ± 126	488 ± 301
$AUC_{0-\infty}$ (ng•ml/hr) (adjusted)	279 ± 99	423 ± 239	319 ± 128	491 ± 284	308 ± 126	481 ± 293
C_{max} (ng/ml)	3.4 ± 1.1	5.0 ± 2.7	4.0 ± 1.5	5.8 ± 2.9	3.7 ± 1.3	5.7 ± 3.3
T_{max} (median hours)	36.0	48.0	48.0	48.0	48.0	48.0

The buttock and the hip application sites were determined to be bioequivalent to the abdominal application site based on the 90% confidence intervals (CI) of 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).

	Buttock:Abdomen		Hip:Abdomen	
Parameter	Ratio	90% CI	Ratio	90% CI
C_{max}	1.1519	1.0668, 1.2439	1.0802	1.0005, 1.1661
$AUC_{0-\infty}$,	1.1361	1.0641, 1.2129	1.0891	1.0203, 1.1625
$AUC_{0-\infty}$ (adjusted)	1.1428	1.0696, 1.2210	1.0954	1.0255, 1.1702

Secondary Variables: Residual analysis of the used systems indicated that the systems applied to the abdomen, buttocks, and hip delivered 13.1, 15.5, and 14.1 mg oxybutynin/96 hours, respectively (overall, 3.6 mg/day). When estimated using $AUC_{0-\infty}$ values, the systems applied to the abdomen, buttocks, and hip delivered 9.5, 10.9, and 10.5 mg oxybutynin/96 hours, respectively (overall, 2.6 mg/day).

Skin tolerability was good to excellent at all three application sites with all evaluations indicating either no erythema or mild erythema 1 and 24 hours after system removal. No severe erythema was observed and no subjects complained of skin-associated problems.

System adherence was good for all systems at all three application sites with greater than 99% of all evaluations graded as 4 (indicating > 90% adhesion).

Safety Results: When all adverse events, regardless of causality, were considered, 50% (12/24) of the subjects experienced one or more adverse events in any system organ class. The most frequently reported adverse events (> 5%), regardless of causality, were diarrhea in five (21%), headache in three (13%), dry mouth in two (8%), and rhinitis in two (8%) subjects. When only treatment-related adverse events were considered, 29% (7/24) of the subjects experienced one or more adverse events. The most frequently reported treatment-related adverse events (> 5%) were headache in three (13%) and dry mouth in two (8%) subjects. All events resolved without sequelae. No subjects were withdrawn from the study for adverse-related events.

CONCLUSIONS:

Plasma concentrations of oxybutynin and N-desethyloxybutynin were comparable to previous studies and within the range of therapeutically effective concentrations in the prior phase II trial. The plasma concentration profiles were similar and pharmacokinetic parameters bioequivalent for the hip and buttock compared to the abdomen. As with prior studies, plasma concentrations were sustained over the 96 hour dosing interval, supporting the anticipated twice weekly application regimen. The bioequivalence of the three application sites supports the clinical use of all three application. This allows rotation of transdermal system application sites for optimal system tolerability and patient convenience during long-term use. The oxybutynin matrix system exhibited good adherence, was well tolerated and was not associated with any adverse trends in any safety parameters.

Date of the Report: August 9, 2000

STUDY O99007

Name of Sponsor/Company: Watson Laboratories, Inc. - Utah, Salt Lake City, Utah 84108	**Location of Full Report in the Submission**	***(For National Authority Use only)***
Name of Finished Product: Oxybutynin matrix transdermal system	**Volume:**	
Name of Active Ingredient(s): Oxybutynin	**Page:**	

Title of Study: Steady-State Pharmacokinetics And Dose Proportionality Of Oxybutynin Following Multiple Transdermal Applications In Healthy Volunteers

Investigators:

Study Center(s):

Studied period (years): 2000 **(date of first enrollment):** 06 February 2000 **(date of last completed):** 17 March 2000	**Phase of development:** Phase I

Objectives: The primary objectives of this study were to evaluate and compare the steady-state pharmacokinetics and metabolism of oxybutynin administered as multiple 13, 26, and 39 cm^2 transdermal systems applied to the abdomen and to evaluate the dose-proportionality of rising oxybutynin doses. Secondary objectives were to: (a) to assess the local skin tolerability of the transdermal system, and (b) to evaluate the adhesion properties of the system.

Methodology: This was a randomized, open-label, three-way crossover study. Subjects were assigned to receive the three study treatments (Treatments A, B, and C) in randomized sequence with each subject receiving each study treatment once. Serial blood samples were collected for analysis of plasma oxybutynin and N-desethyloxybutynin (DEO) concentrations.

The treatment phase consisted of three study periods (Periods I, II, and III). Each treatment period consisted of the sequential application to the lower abdomen of three 13, 26, or 39 cm^2 oxybutynin systems according to the randomization schedule. The first two systems were applied for 84 hours each; the third system was applied for 96 hours. Blood samples were collected on an out-patient basis at predefined times over the next 288 hours. The start of each study period was separated by 14 days. The duration of the entire study (excluding the screening visit) was 6 weeks for each subject.

Number of patients (planned and analyzed): Number planned: 24; Number enrolled: 26 (13 male, 13 female); Number analyzed: 23 for pharmacokinetics, 26 for safety.

Diagnosis and main criteria for inclusion: Healthy males and females, age 18 or older; Body Mass Index ≥ 20 and ≤ 28 and weight ≥ 50 and ≤ 90 kg; willing and able to sign the consent form.

Test product, dose and mode of administration, batch number: 13, 26 and 39 cm^2 oxybutynin transdermal systems, control numbers 99Z133, 99Z13, and 99Z137, respectively.

Duration of treatment: 6 weeks overall (84 hours for each of the first 2 systems, 96 hours for the 3rd system)

Criteria for evaluation: **Primary variables:** Plasma concentrations of oxybutynin and DEO were measured in serially collected blood samples, 0 (within 30 minutes prior to each system application), 84, 168, 169, 170, 172, 174, 176, 178, 180, 192, 204, 216, 228, 240, 252, 264, and 288 hours

following application of the first system.

Secondary variables: Total oxybutynin delivery from the 3rd system at each dose level was estimated over its 96 hour wear period from the difference in measured oxybutynin content of used systems and mean content of control systems and from AUC_{0-96} values. Local skin tolerability was evaluated immediately , one, and 24 hours after removal of the 3rd system at each dose level. Adherence of the first 2 systems to the skin was evaluated immediately prior to their removal. Adherence of the 3rd system was evaluated 12 hours after application, and daily, prior to each blood collection during the system wear period.

Safety: Safety assessments included pre- and post-treatment physical examinations, pre-study clinical laboratory tests, and monitoring of adverse events. Each adverse event was evaluated for duration, intensity, and its relationship or association to the test articles.

Statistical Methods: The primary pharmacokinetic end-points were oxybutynin and DEO C_{max}, T_{max}, and AUC_{0-96} over the 96 hours following application of the 3rd system in each treatment group, and dose proportionality of the three system sizes. Secondary end-points included plasma oxybutynin and DEO C_{max} and T_{max} after application of each study system, and estimated oxybutynin delivery based on system depletion analysis and AUC_{0-96} values.

Plasma concentration-time profiles for oxybutynin and DEO were characterized in terms of AUC_{0-96}, C_{max}, and T_{max}. C_{max} and T_{max} for the 3rd application in each treatment group were obtained by direct observation of the concentration-time curves. AUC_{0-96} was calculated using the trapezoidal method from time 0 to 96 hours. Overall dose proportionality of AUC_{0-96} was determined using the classical weighted regression approach. For the dose-proportionality analysis, values from the 39 cm^2 system were used as reference. Attainment of steady-state was assessed by comparing the plasma concentrations at the 84 hour dosing points from application 2 and 3 with the plasma concentrations at the 84 hour dosing point from the 1st application using a paired t-test. Non-parametric Wilcoxon paired signed rank tests were conducted to compare T_{max} values between treatments.

Descriptive statistics of system adhesion and safety data, including assessment of application site skin tolerability and adverse events, were tabulated.

RESULTS: **Primary Variables:** Mean plasma oxybutynin concentrations following application of the 13 and 39 cm^2 systems reached steady state concentrations during the 1st system application and were maintained during the wear periods for the 2nd and 3rd systems. Steady-state plasma oxybutynin concentrations following application of the 26 cm^2 system were achieved during the 2nd application, with somewhat lower concentrations measured during the 1st system application. Plasma oxybutynin and DEO concentrations, as well as pharmacokinetic parameters, increased in a linear fashion with increasing dose. Oxybutynin pharmacokinetic parameters are presented in the table below.

PK Parameter (mean ± SD)	13 cm^2	26 cm^2	39 cm^2
C_{max} (ng/ml)	2.3 ± 0.8	4.4 ± 1.3	6.6 ± 2.4
AUC_{0-96} (ng•ml/hr)	143 ± 39	274 ± 59	408 ± 108
AUC_{0-96} (ng•ml/hr) (dose normalized)	429 ± 118	410 ± 89	408 ± 108
T_{max} (median hours)	10.0	10.0	10.0

Secondary Variables: Residual analysis of the used systems indicated that the 3rd lower abdominal application of the 13, 26, and 39 cm^2 systems delivered 5.8, 11.1, and 16.0 mg oxybutynin/96 hours, respectively. When estimated using AUC_{0-96} values and published drug clearance, estimated doses were 4.9, 9.3, and 13.9 mg for the 3 system sizes, respectively.

Skin tolerability was good to excellent for all applications with a majority of all evaluations indicating either no erythema or mild erythema immediately after system removal. No severe erythema was observed and no subjects complained of other skin-associated problems.

System adherence was good for all systems with greater than 90% of all evaluations graded as 4 (indicating > 90% adhesion).

Safety Results: When all adverse events, regardless of causality, were considered, 96% (25/26) of the subjects experienced one or more adverse events in any System Organ Class. When only treatment-related adverse events were considered, 81% (21/26) of the subjects experienced one or

more adverse events. The most frequently reported adverse events (> 10%), regardless of causality and system size, were application site reactions (primarily mild erythema and pruritus), headache, and pharyngitis. There were no differences in adverse event frequency between the three system sizes. All events resolved without sequelae. No subjects were withdrawn from the study because of adverse events.

DISCUSSION AND CONCLUSIONS: Plasma concentrations, pharmacokinetic parameters, and estimated doses of oxybutynin were proportional to surface area for the 13, 26, and 39cm^2 TDS. Steady-state conditions were attained during the first system application, with no evidence of drug accumulation with repeated application. These results are consistent with published reports on oxybutynin pharmacokinetics following oral and intravenous administration.[1] As with prior investigations on the oxybutynin TDS, the matrix systems exhibited good adherence, were well tolerated, and were not associated with any adverse trends in the evaluated safety parameters.

Date of the Report: October 9, 2000

Date of Revision: February 7, 2001

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STUDY O99009

Name of Company: Watson Laboratories, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Oxybutynin TDS		
Name of Active Ingredient(s): Oxybutynin		

Title of Study: 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

Investigators and Study Centers:
40 sites (see Appendix 16.1.4)

Publication (reference):
None

Study Period (years): 1 year (12 weeks double-blind [DB] period, 12 weeks open-label [OL] safety period, 28 weeks OL extension) Date of first enrolled: 21-DEC-99 Date of last completed: 26-JUL-00 (DB); 09-OCT-00 (OL)	**Clinical Phase:** III

Objectives: The primary objective of the double-blind period of the study was to compare the safety and efficacy of three doses of Oxybutynin Transdermal Systems (TDS) with placebo during 12 weeks of treatment. The primary efficacy endpoint was the change from baseline to endpoint in the double-blind period in the number of incontinent episodes recorded in the 7-day urinary diary. The secondary objectives of the double-blind period included comparisons of daily urinary frequency, urinary volume per void, quality of life (QoL) scores, Global Assessment of Disease State, as well as safety assessments. In addition, plasma concentrations of oxybutynin and its primary active metabolite were measured to evaluate population pharmacokinetics.

The objectives of the open-label safety period included characterization of the distribution of doses used by the patients in the study, confirmation of continued efficacy using both objective and subjective measures, and continued treatment safety in approximately 300 patients. Changes in QoL scores over the 12-week open-label safety period were also evaluated, and plasma concentrations of oxybutynin and its primary active metabolite were measured.

The objective of the 28-week open-label safety extension was to demonstrate continued treatment safety in approximately 100 patients who had been exposed to the Oxybutynin TDS for 1 year.

Methodology: This study consisted of three periods for a total study duration of 1 year: (1) a 12-week, double-blind, placebo-controlled period evaluating three doses of Oxybutynin TDS, followed by (2) a 12-week, open-label, dose-titration safety period, and (3) a subsequent 28-week, fixed-dose, open-label safety extension.

The double-blind period was designed as a multi-center, randomized study conducted in patients with overactive bladder who exhibited symptoms of urge incontinence and urinary frequency. The double-blind period consisted of a screening period of 3 to 4 weeks duration and a randomized, double-blind, placebo-controlled treatment period (12 weeks). The screening period included a 2-week period for washout from current pharmacological treatment and for practice of bladder and fluid management techniques taught to all patients at the first study visit, a 1-week baseline evaluation to allow for completion of the 7-day urinary diary, and an additional 1-week period, if necessary, to repeat the 7-day urinary diary.

Patients who met the eligibility criteria during the screening and baseline evaluations were randomized to one of the following treatment groups: 13 cm^2 Oxybutynin TDS, 26 cm^2

Name of Company: Watson Laboratories, Inc.	Individual Study Table Referring to Part of the Dossier:	*(For National Authority Use Only)*
Name of Finished Product: Oxybutynin TDS	Volume:	
Name of Active Ingredient(s): Oxybutynin	Page:	

Oxybutynin TDS, 39 cm^2 Oxybutynin TDS, or placebo TDS. Doses were obtained using combinations of active and placebo 13 cm^2 and 26 cm^2 systems. All patients applied two systems, twice weekly (approximately every 3.5 days), to the abdomen for a total of 12 weeks. The active TDS delivered a nominal dose of 0.1 mg oxybutynin/cm^2 surface area per day.

The target enrollment in the study was approximately 450 patients at 40 centers in the double-blind period to provide 400 patients evaluable for efficacy at the end of the 12 weeks of treatment. Patients who completed the double-blind period were eligible to enter the 12-week open-label, dose-titration safety period. In the open-label safety period, all patients began treatment with a single 13 cm^2 Oxybutynin TDS applied twice weekly. The dose of medication was titrated by the investigator after 2 and 4 weeks of treatment based on the patient's symptoms and remained fixed for the last 8 weeks.

Patients who completed the 12-week open-label safety period had the option to continue into a 28-week, open-label, fixed-dose safety extension. Participation was limited to approximately 150 patients from the top-performing sites in order to ensure exposure in 100 patients. The results of the 28-week open-label safety extension will be reported separately.

Number of Patients (Planned and Analyzed):

Study Period	Planned to enroll/complete	Enrolled & Completed	Analyzed	
			Efficacy	Safety
Double-blind	Appr. 450/400	520 & 447	515 (mITT[1])	520
12-Week open-label	Appr. 300/300	411 & 358	385	411
28-Week extension	Appr. 150/100	The results will be reported separately.		

[1] Six patients were misrandomized during the double-blind treatment period. They were included in the mITT cohort by the treatment actually received. The ITT cohort includes these patients by randomized treatment assignment.

Diagnosis and Main Criteria for Inclusion:

Overactive bladder with symptoms of urgency, urge urinary incontinence, and urinary frequency that was not related to chronic illness, anatomical weakness or abnormalities, or medication use.

Test Product, Dose and Mode of Administration, Batch Number:

Double-blind period: Oxybutynin TDS, 13 cm^2 (Lot 99Z173) and 26 cm^2 (Lot 99Z178), and matching placebo systems (13 cm^2 = Lot 99Z125 and 26 cm^2 = Lot 99Z115) were administered as transdermal patches to the abdomen.

Open-label safety period: Oxybutynin TDS 13 cm^2 (Lot 99Z173), 26 cm^2 (Lots 99Z178 and 99Z162), and 39 cm^2 (Lots 99Z183 and 99Z167) were administered as transdermal patches to the abdomen.

Duration of Treatment:

24 weeks (12 weeks for the double-blind period followed by 12 weeks for the open-label safety period) followed by 28 weeks of open-label extension.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo TDS, 13 cm^2 (Lot 99Z125) and 26 cm^2 (Lot 99Z115) containing adhesive matrix only

Criteria for Evaluation:

Efficacy: The primary measurement used to determine efficacy in the double-blind period was the change from baseline (Visit 3) to endpoint (Week 12, Visit 7 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. For the open-label

safety period, change from baseline to endpoint (Week 24, Visit 10 or LOCF) for the primary measurement was analyzed by final dose group. Supporting measurements of efficacy included changes in average daily urinary frequency and average urinary volume per void from baseline to endpoint along with the Global Assessment of Disease State and three QoL instruments, the Short Form 36 (SF-36), the Incontinence Impact Questionnaire (IIQ), and the Urogenital Distress Inventory (UDI).

Safety: Measurements of safety included physical examination, incidence and severity of adverse events (AEs), clinical laboratories and urine beta-human chorionic gonadotropin (β-HCG) (for females of childbearing potential), serum prostate specific antigen (PSA) (males only), post-void residual (PVR) urine volume measurements, electrocardiogram (ECG), and skin tolerability assessment.

Statistical Methods : Four patient populations were defined for statistical analysis and data tabulation: the Safety cohort, the modified Intent-To-Treat (mITT) cohort, the Intent-To-Treat (ITT) cohort, and the Evaluable cohort. Two datasets were defined as observed cases (OC) and LOCF. Patient demographic and physical characteristics and safety data were summarized for each analysis cohort and treatment group.

The primary efficacy analysis compared the change in number of urinary incontinence episodes per week from baseline to endpoint using LOCF imputation for patients who did not complete the double-blind period. The number of episodes was obtained from the 7-day urinary diary and was normalized to a 7-day value for patients with < 7 days of recorded data. This parameter was analyzed by an analysis of covariance (ANCOVA).

Supporting efficacy analyses compared the mean change in average daily urinary frequency and the mean change in average urinary volume per void from baseline to endpoint using LOCF imputation for patients who did not complete the double-blind period. Additional supporting efficacy analyses compared the mean Global Assessment of Disease State at baseline to endpoint and the mean change in the Global Assessment of Disease State at baseline to endpoint. Average daily urinary frequency was calculated by dividing the total number of events recorded in the 7-day urinary diary by the total number of days. Average urinary volume per void was calculated by dividing the sum of the voided volumes by the total number of voids recorded in the 2-day urine volume documentation. Quality of life was assessed using three validated questionnaires: the SF-36, the IIQ, and the UDI. The mITT cohort was used for the statistical analysis of the QoL data.

RESULTS

Efficacy: In the double-blind period, patients treated with the 39 cm^2 TDS experienced a statistically significant decrease in the number of urinary incontinence episodes per week from baseline to endpoint compared with placebo (the primary endpoint). The median number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week, or nearly 3 episodes per day, compared with the median decrease of 14.5 episodes per week in the placebo group. Statistically significant improvements were also observed in the average daily urinary frequency (median decrease of 2 episodes per day) and the average urinary volume per void (median increase of 24 mL per void) in the 39 cm^2 group compared with placebo.

Patients treated with the 26 cm^2 TDS also showed significant improvements in the volume of

urine per void and a trend toward improvement in the number of urinary incontinence episodes per week and average daily urinary frequency compared with placebo. The median increase in voided volume in the 26 cm^2 group was 19 mL at endpoint compared with 6 mL for placebo. The third supporting endpoint, the Global Assessment of Disease State, proved unable to distinguish among the different treatments. The incontinence-specific quality of life measure, the IIQ, indicated a significant positive effect of the 39 cm^2 treatment on IIQ total score at all study visits in comparison with placebo. This effect was also demonstrated for several IIQ subscales at various post-baseline time points. In general, treatment with the 13 cm^2 and 26 cm^2 systems showed similar trends as seen with the 39 cm^2 systems in most parameters, but the magnitude of change was frequently not significant when compared with placebo response.

Response to TDS treatment continued in the open-label safety period with patients choosing final treatment levels that allowed them to attain roughly similar levels of response across final dose groups. The choice of a final treatment dose was not obviously influenced by the assigned dose level in the double-blind period.

Safety: Adverse events were reported by > 50% of patients during both the double-blind and open-label periods of the study; however, most AEs were judged as not related to treatment. The most frequently reported treatment-related AE during both the double-blind and open-label periods was application site pruritus. The most common anticholinergic AE reported in both the double-blind and open-label periods was dry mouth. Dry mouth occurred with approximately equal frequency in patients who received both placebo (8.3%) and active treatment (7.0%).

Fifty-three (10.2%) patients discontinued participation in the double-blind period due to AEs, and 30 (7.3%) patients discontinued during the open-label safety period due to AEs. Most of these patients (77.4% in the double-blind and 82.4% in the open-label period) discontinued due to AEs that were drug-related, most commonly application site reactions.

Most AEs were mild to moderate in severity; however, some patients experienced severe, drug-related AEs, most of which occurred at the application site. Application site reactions appeared more frequently in patients who received the 39 cm^2 dose for both the double-blind and open-label periods.

No deaths occurred during either the double-blind or open-label periods of the study. However, one patient died after completion of the open-label safety period due to a malignant mixed Müllerian tumor. Fourteen (2.7%) patients experienced 18 serious adverse events (SAEs) during the double-blind period, and 7 (1.7%) patients experienced 9 SAEs during the open-label safety period. None of these events was considered to be related to study drug, and most were resolved prior to patient discharge from the study.

There were no adverse trends observed in any of the safety parameters monitored during the study. There were no marked differences in the mean and median values for hematological, serum chemistry, or urinalysis parameters at any visit, or at endpoint between the treatment groups or within the treatment groups across visits. In addition, no adverse trends were noted in vital signs or physical examination findings between the treatment groups or within the treatment groups across visits.

Oxybutynin TDS was well-tolerated by most patients with the majority (≥ 86%) of patients on both active treatment and placebo experiencing either no erythema or mild erythema at the

application sites during the study. In patients who experienced erythema in either period, the most common severity classification was mild.

CONCLUSION

Oxybutynin TDS administered in two dosage strengths, 26 cm^2 and 39 cm^2, in a twice-weekly regimen was shown to be effective, safe, and well-tolerated during chronic treatment in patients with overactive bladder.

The significant reductions and trends observed in the number of incontinence episodes, urinary frequency, increase in void volume, incontinence-specific quality of life evaluations, the range of individual patient response, and the dose titration in the open-label safety period support the efficacy of the 26 cm^2 and 39 cm^2 systems. The large placebo response obscured treatment effects for the Global Assessment of Disease State.

The most common drug-related AEs, dry mouth and application site pruritus, were consistent with the AE profile of anticholinergic and transdermal products. Transdermal oxybutynin treatment was associated with a low incidence of anticholinergic AEs. The TDS was shown to have good skin tolerability as most patients (≥ 86%) experienced no erythema or mild erythema at the application sites.

No deaths occurred during the study. None of the SAEs reported was considered by the investigator to be related to treatment and most resolved prior to study completion.

No unexpected findings or adverse trends in vital signs, ECGs, and clinical laboratory parameters over a 24-week treatment period with Oxybutynin TDS confirm the safety profile of transdermal oxybutynin.

Date of the Report: 13-MAR-01

Synopsis

Name of Sponsor/Company: TheraTech, Inc. Salt Lake City, Utah 84108	**Location of Full Report in the Submission**		*(For National Authority Use only)*
Name of Finished Product: — Oxybutynin Matrix Delivery System			
Name of Active Ingredient(s): Oxybutynin			
Title of Study: A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-TITRATION STUDY OF THE EFFECT OF ORAL (DITROPAN®) VERSUS TRANSDERMAL (—) OXYBUTYNIN IN PATIENTS WITH URGE INCONTINENCE			
Investigators: 1			
Study Centers:			
Studied period (years): 1997 – 1998 **(date of first enrollment):** October 6, 1997 **(date of last completed):** December 16, 1998		**Phase of development:** Phase II	
Objectives: The primary objective was to compare the efficacy in treatment of urge urinary incontinence between transdermal delivery of oxybutynin by the — matrix system and oral administration of oxybutynin. Evaluation was based on the percentage of responders in each treatment group. Patients were categorized as responders or non-responders to treatment based on the difference in the number of incontinent episodes reported prior to and during treatment. Responders were patients who demonstrated a ≥ 30% decrease from baseline to endpoint in the number of daily incontinence episodes during treatment.			
Secondary: The secondary objectives of this study were to compare the patients' subjective perception of the severity of urinary incontinence, urodynamic parameters and side-effect profile between oral and transdermal administration of oxybutynin. Key secondary parameters included patient reporting of the anticholinergic symptom of dry mouth, a visual analog scale rating of overall efficacy in controlling incontinence, and two cystometric measurements (volume at first desire to void, maximum bladder capacity).			
Methodology: This study was a multi-center, randomized, double-blind, controlled, dose-titration Phase II study. Eligible participants were patients diagnosed with urge incontinence associated with detrusor instability or detrusor hyperreflexia who had symptomatic improvement on prior treatment with oral oxybutynin. A total of 70 evaluable patients were expected to complete the study. Each eligible patient completed a urinary diary, an Anticholinergic Symptoms and Efficacy Questionnaire, and underwent a physical examination during baseline evaluation followed by a washout period of 1-2 weeks from current oral oxybutynin therapy (pretreatment period). Patients whose symptoms of incontinence worsened during discontinuation of oral oxybutynin underwent a cystometrogram and were eligible for the treatment phase. The two treatments included transdermal systems applied twice weekly (every 3.5 days) and oral capsules taken 2-3 times daily for 6 weeks. Each treatment included matching placebo and active formulations. Treatments were randomly assigned in a 1:1 ratio of transdermal:oral therapy. The dose of oxybutynin was titrated at the completion of 2 and 4 weeks of treatment based on the incidence and severity of adverse events. Patients completed a urinary diary and Anticholinergic Symptoms and Efficacy Questionnaire at the			

end of Weeks 2, 4 and 6, and underwent physical examination and cystometry at the end of the treatment phase. Treatment efficacy was determined based on the number of incontinence episodes at Week 6 compared to the pretreatment period. Statistical analysis was conducted to evaluate equivalence in efficacy between transdermal and oral oxybutynin therapy. Patient questionnaires on side effects, urodynamic variables, adverse events, skin tolerability, adhesive properties of the transdermal system, and plasma concentrations of oxybutynin were also evaluated.
Number of patients (planned and analyzed): Planned for Completion = 70 Screened = 91, Enrolled = 76, Evaluable = 72
Diagnosis and main criteria for inclusion: Urge incontinence with detrusor instability or hyperreflexia, age ≥ 18 years, history of response to oxybutynin, current use for at least 6 weeks at dose ≥ 20 mg/day
Test product, dose and mode of administration, batch number: [redacted] oxybutynin transdermal system (#97Z002) and matching placebo (#96Z203)
Duration of treatment: 6 weeks
Reference therapy, dose and mode of administration, batch number: Over-encapsulated Ditropan® tablets (one-half tablet or diluent only placed into each capsule) Lot #98056601 Expiration Date: 2/99
Evaluation of efficacy: Primary Parameter: The percentage of patients categorized as responders to treatment in each study group after a minimum of 4 weeks of treatment was established as the primary efficacy parameter. Secondary Parameters : Secondary efficacy parameters, itemized below, included a subjective overall rating of the efficacy of treatment based on current symptoms experienced by the patients and objective measures derived from the cystometrogram performed upon completion of treatment. 1) Visual analogue overall symptom scoring for urinary incontinence (leakage). 2) Maximum cystometric capacity (ml). 3) Volume at first detrusor contraction (ml). Response to treatment in secondary endpoints was evaluated as the change from baseline to endpoint.
Evaluation of safety: Safety evaluations included the Anticholinergic Symptoms and Efficacy Questionnaire, physical examinations, serum chemistries, urinalyses, and adverse event records. Dermatologic evaluations of the patch application sites were performed at the end of Weeks 2, 4 and 6 of the treatment phase.
Statistical methods: Primary Efficacy Analysis Variable: Subjects were categorized as responders or non-responders to treatment based on the difference in the number of incontinent episodes reported prior to and during treatment. Responders were subjects who demonstrated a ≥ 30% decrease from washout to endpoint in the number of daily incontinence episodes during treatment. This dichotomous response variable was the primary efficacy variable for the study. Primary Analysis Methods: The primary statistical analysis was conducted to evaluate equivalence in efficacy of transdermal versus oral oxybutynin. A 95% confidence interval for the difference in proportion of responders between transdermal and oral oxybutynin was calculated using a normal distribution approximation with estimates of standard errors based on observed proportions (9,10). Equivalence was defined to be demonstrated when the 95% confidence interval for the difference in proportions of responders was completely contained in the interval (-15%, 15%). Secondary Efficacy Analysis Variables: Response to treatment in secondary endpoints was evaluated as the change from pretreatment to endpoint. Secondary endpoints included the following: analog score for urinary incontinence from the Anticholinergic Symptoms and Efficacy Questionnaire, volume at first involuntary contraction, maximum cystometric capacity, and number of daily incontinence episodes. Secondary Analysis Methods: Comparisons of change from pretreatment to endpoint between transdermal and oral oxybutynin treatments were performed using two-sample, two-sided t-tests for continuous variables and Wilcoxon rank sum tests for ordinal variables. Comparisons of pretreatment to endpoint levels were conducted separately within each treatment group, using Wilcoxon paired signed rank tests for frequency of urinary incontinence and paired t-tests for analogue scores for incontinence, volume at first contraction, and maximum cystometric capacity. A plot of mean daily incontinence episodes was constructed by visit and treatment regimen. Anticholinergic Symptoms and Efficacy Questionnaire: Frequency distributions for symptom occurrences and level of intensity were reported by treatment regimen. A plot of the percentage of subjects with dry mouth was reported by treatment. In addition, a χ^2 test of treatment regimen association with dry mouth was conducted.
Patient Disposition and Demographics: Two patients were withdrawn after the fourth week, one from each

treatment group. Patient #22 dropped from the oral treatment group due to intolerable dry mouth. Patient #67 withdrew from the study for personal reasons, relocation away from the study center. The patients participating in the study were primarily elderly Caucasian women (oral group: mean age = 63 yrs, 95% Caucasian, 97% female; transdermal group: mean age = 64 yrs, 95% Caucasian, 87% female).

Treatment Compliance: > 96% of expected doses of both oral capsule and transdermal systems were used by patients in both treatment groups.

Efficacy Results:

1) 87% of transdermal treatment patients responded to treatment versus 89% in the oral group, yielding a 95% confidence interval for the mean difference of −17% to +13%.
2) Average (SD) incontinent episodes decreased from washout to Week 6 in both treatment groups: transdermal from 7.3 (4.5) to 2.4 (2.4); oral from 7.4 (4.1) to 2.6 (3.3).
3) Patient rated (visual analog scale) control of urinary leakage significantly was reduced by both treatment comparing washout to last visit ($p<0.0001$), with no difference between treatments ($p=0.9$).
4) Cystometry in both treatment groups reflected expected changes with oxybutynin treatment, increased volume to first detrusor contractions and increased maximum bladder capacity.

Safety Results: Incidence of dry mouth symptoms based on anticholinergic questionnaire were significantly lower in the transdermal treatment group (38%) compared to the oral group (94%), $p<0.001$. The majority of patients in the transdermal group with dry mouth reported improved symptoms compared to prior treatment (67%). Of 223 total adverse events related to treatment (including adverse events and anticholinergic symptoms), 149 occurred in the oral group and 74 in the transdermal group. The majority were anticholinergic symptoms. Skin tolerability of the transdermal systems was excellent: >90% of tolerability ratings indicated none or mild erythema at the application site. Three patients had adverse events related to application site reactions. One patient developed allergic contact dermatitis to the patch, confirmed by rechallenge to be due to topical oxybutynin (negative reaction to placebo patch); however, the patient continued on oral oxybutynin treatment after the study withoutsequelae. The treatments had no apparent effects on other safety parameters (physical examination, laboratory tests, etc.)

Conclusions: Transdermal oxybutynin for the treatment of urge urinary incontinence represents an important therapeutic innovation. The incidence and severity of dry mouth, the primary anticholinergic side effect associated with treatment, were significantly improved compared to treatment with the oral, immediate-release product. Transdermal treatment achieved comparable efficacy to oral treatment which included overall patient response to treatment, number of incontinent episodes, and influence of treatment on urinary cystometry parameters. Phase III development activities are clearly supported by the results of this study.

Date of the report: May 12, 1999

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Pharmacometrics consultation note:

He Sun, Ph.D.

NDA 21-351 Oxybutynin

Overall, the pharmacometrics reviewer agrees the sponsor's conclusion.

A population pharmacokinetics analysis was conducted for data collected from a multi-center clinical trial, study O99009, to check for the effect of Age, Weight, and Gender on the mean oxybutynin and its metabolite DEO.

Nonlinear mixed effect modeling analysis was not used and was not needed in this data analysis since the concentrations across various time points are constant when the transdermal system was applied to patients. Instead, analysis of covariance (ANOCOVA) was applied to data.

Data visual inspection does not suggest any age, body weight and gender effects on the steady-state concentrations of oxybutynin and its metabolite DEO. Statistic regression and ANOCOVA analyses confirmed the conclusion.

Cover sheet and OCPB filing/review form

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-351	*Brand Name*	OXYTROL
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Oxybutynin transdermal system
Medical Division	DRUDP (HFD 580)	*Drug Class*	Urinary incontinence
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Overactive bladder with urge incontinence, urgency & frequency
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Transdermal Patch
Date of Submission	4/26/2001	*Dosing Regimen*	Twice weekly (every 3 to 4 days)
Estimated Due Date of OCPB Review	1/20/2002	*Route of Administration*	Transdermal
PDUFA Due Date	2/26/2002	*Sponsor*	Watson Labs (Utah)
Division Due Date	2/12/2002	*Priority Classification*	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	6		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	6			

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Is the 'to-be-marketed' formulation the same as the 'clinical trial formulation'? Answer : Yes (also see below)**	
Other comments or information not included above	**In the pivotal clinical trial, sponsor evaluated the safety/efficacy of simultaneous 13 cm^2 + 26 cm^2 patches in lieu of a single 39 cm^2 patch, and wish to market a single 39 cm^2 patch. The sponsor has submitted dose proportionality data between the13 cm^2, 26 cm^2 & 39 cm^2 patches, as well as compared the plasma levels of drug and metabolite following administrations of simultaneous 13 cm^2 + 26 cm^2 patches (double blind portion of trial) versus one 39 cm^2 patch (open label extension of trial) . Based on these submitted data, application is filable.**	
Primary reviewer Signature and Date	**Dhruba J. Chatterjee, Ph.D.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, Ph.D.**	

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

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/s/

Young-Moon Choi
3/22/02 12:15:46 PM
BIOPHARMACEUTICS

Ameeta Parekh
3/22/02 03:33:11 PM
BIOPHARMACEUTICS
I concur