

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-351

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-351
Review number: 1
Serial number/date/type of submission: Original NDA/April 26, 2001
Information to sponsor: Yes () No (X)
Sponsor and/or agent: Watson Labs
Manufacturer for drug substance :

Reviewer name: Alex Jordan
Division name: DRUDP
HFD #: 580
Review completion date: February 12, 2002

Drug:

Trade name: Oxytrol
Generic name (list alphabetically): oxybutynin transdermal system
Code name:
Chemical name: 4-(Diethylamino)-2-butyn-1-yl-phenylcyclohexylglycolate
CAS registry number: 5633-20-5
Mole file number:
Molecular formula/molecular weight: MW 357. —
Structure:

Relevant INDs/NDAs/DMFs:

Drug class: anticholinergic, antispasmodic

Indication: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Clinical formulation: Oxybutynin TTS consists of a — backing film and a matrix adhesive layer containing

as a — (te). Triacetin, USP (ester of glycerin and acetic acid) acts
3.9 mg oxybutynin/day Sponsor is seeking approval of — 1.39 cm² releasing

Route of administration: dermal

Proposed use:

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: Oxybutynin hydrochloride is an aminoacetylene compound that has been on the market in the US for the treatment of uninhibited neurogenic bladder and reflex neurogenic bladder since 1975. Oxybutynin has anti-cholinergic effects that inhibit involuntary bladder contraction via pelvic splanchnic nerve stimulation. It also affects the membrane-dependent Ca channel of bladder smooth muscle to relax

bladder smooth muscle and increase bladder capacity by inhibiting rhythmic contraction under the full bladder condition.

Safety evaluation: The transdermal route of administration avoids the significant presystemic metabolism that occurs following oral administration. This results in increased bioavailability of the parent compound and a significant reduction in circulating N-desethyloxybutynin, the primary active metabolite that has been associated with anticholinergic side effects. Transdermal delivery also leads to sustained plasma concentrations of oxybutynin, reducing the peak to trough changes that occur following oral dosing.

Because the sponsor did not submit data for plasma oxybutynin levels following multiple oral doses, the Biopharmaceutics reviewer used computer modeling to compare the TDS 3.9 mg/day system (39 cm²) to 5 mg QID oral oxybutynin and estimated that the AUC of oxybutynin was 408 for the patch compared to 224 ng.hr/ml following oral administration. The C_{max}'s were similar (6.6 ng/ml vs. 7.4 ng/ml). The TDS had lower plasma levels of the metabolite desethyloxybutynin (8.5 vs. 41.0 ng/ml for the C_{max} and 2528 vs. 561 ng.hr/ml for the AUC's).

The sponsor states that no unusual metabolites were formed from the dermal route of administration but I could find no evidence that total metabolites had been investigated. The ingredients of the transdermal patch pose no unusual safety concerns.

Safety issues relevant to clinical use: None

Other clinically relevant issues: None

Conclusions: The oxybutynin transdermal patch has no preclinical safety issues.

Communication review:

Labeling review: Under Carcinogenesis, Mutagenesis, Impairment of Fertility: The first sentence should be changed to "A 24-month study in rats at doses of oxybutynin chloride of 20, 80 and 160 mg/kg

— .) showed no evidence of carcinogenicity."

Under Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride given orally to the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride.

RECOMMENDATIONS: The oxybutynin transdermal system is approvable from the standpoint of Pharmacology.

Internal comments:

External recommendations (to sponsor):

Draft letter content for sponsor (if not same as above):

NDA issues:

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc: list:

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

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Studies reviewed within this submission:

Studies not reviewed within this submission:

Introduction and drug history:

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PHARMACOLOGY:

Primary pharmacodynamics: No pharmacology data submitted

Mechanism of action:

Drug activity related to proposed indication:

Secondary pharmacodynamics:

Pharmacology summary:

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Pharmacology conclusions:

SAFETY PHARMACOLOGY:

Only summaries submitted. No unusual or unexpected effects.

Neurological effects:

Cardiovascular effects: Increase in respiration rate at 100 mg/kg in rats; increase in heart rate at 100 mg/kg in rats. No effect on respiration rate, BP, HR or ECG in dogs at doses up to 400 mg/kg or in rats at doses up to 100 mg/kg. Drug was administered percutaneously or subcutaneously.

Pulmonary effects:

Renal effects:

Gastrointestinal effects:

Abuse liability:

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Other:

Safety pharmacology summary:

Safety pharmacology conclusions:

**APPEARS THIS WAY
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PHARMACOKINETICS/TOXICOKINETICS:

PK parameters:

Absorption:

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Distribution:

Metabolism: Following percutaneous administration, the main metabolite of oxybutynin in rat and dog plasma is phenylcyclohexylglycolic acid (PCGA), formed by the hydrolysis of oxybutynin's ester bond. The N-desethyl metabolite was not detected in plasma. Following oral administration of 50 mg/kg oxybutynin to rats, no unmetabolized drug was detected in plasma. About 50% of the total radioactivity was the metabolite PCGA. In contrast, unmetabolized substance was detected in plasma after percutaneous administration with plasma PCGA levels being only 10% of that following oral admin.

Only PGCA was detected in plasma of dogs following oral administration of oxybutynin, 5 mg/kg, probably due to first-pass metabolism. In contrast, unmetabolized drug was detected in plasma after subcutaneous administration. Plasma PCGA levels following subcutaneous administration were only 10% of that following oral administration.

Percutaneous administration of oxybutynin to rats and dogs reduces drug metabolism and does not produce any metabolites that were not seen when the drug was given orally. Therefore, the oral toxicology studies are valid for testing the safety of percutaneously administered oxybutynin.

Excretion:

Other studies:

PK/TK summary:

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ON ORIGINAL**

PK/TK conclusions:

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TOXICOLOGY:**Study title:**

The sponsor conducted two nonclinical dermatotoxicity studies of the oxybutynin TDS. They also submitted a number of pharmacology and toxicology studies with oxybutynin, _____ and a review of the literature. I have reviewed these studies briefly. Oxybutynin was administered subcutaneously to rats and dogs at doses up to 48000 mg/kg in rats and 2000 mg/kg in dogs. Studies with sc injected oxybutynin were conducted in rats and dogs for 4 and 13 weeks. In the 4-wk studies, rats received doses up to 600 mg/kg and dogs received doses up to 200 mg/kg. In the 13-week studies, rats were given up to 72 mg/kg/3 days and dogs up to 30 mg/kg/3 days. Pharmacological effects were mydriasis, increased water intake and increased urine volume. Other effects due to drug/vehicle administration on the skin included induration, ulcer, incrustation and increased leukocytes. There was some decrease in weight gain and decreased food intake due to decrease in general health. The NoAEL was considered to be 9 mg/kg/3 days for rats and 6 mg/kg/3 days for dogs.

Key study findings:

Study no: — study 67264

Volume #, and page #: 8/145

Conducting laboratory and location: _____

Date of study initiation:

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle: 10 cm² oxybutynin — GMP transdermal patch.

Methods (unique aspects): two patches were used

Dosing:

Species/strain: New Zealand White rabbits

#/sex/group or time point (main study): 2 males 4 females

Satellite groups used for toxicokinetics or recovery:

Age: young adults

Weight: 3.0-3.2 kg

Doses in administered units: 2 10² cm patches

Route, form, volume, and infusion rate:

Observations and times:

Clinical signs:

Body weights:

Food consumption:

Ophthalmoscopy:

EKG:

Hematology:

Clinical chemistry:

Urinalysis:

Gross pathology:

Organs weighed:

Histopathology:

Toxicokinetics:

Other:

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Results:

Mortality: none
 Clinical signs:
 Body weights:
 Food consumption:
 Ophthalmoscopy:
 Electrocardiography:
 Hematology:
 Clinical chemistry:
 Urinalysis:
 Organ weights:
 Gross pathology:
 Histopathology:
 Toxicokinetics:

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Summary of individual study findings:

Toxicology summary: patches were scored at 24 and 72 hrs. At 24 hrs patch site A erythema was observed in 3/6 animals with scores of 1 to 2. At patch site B, erythema was observed in 6/6 animals with a score of 1 to 2. At the negative control site, there was no dermal irritation.

At 72 hrs, patch site A had the same score, however patch site B had erythema in 6/6 rabbits with a score of 1 to 3 and edema in 4/6 with a score of 1 to 2.

On average the dermal irritation score for patch site A was 0.8 (barely perceptible irritant) and for patch site B it was 1.9 (slight irritant).

Toxicology conclusions:

Study no: — study 67265

Volume #, and page #: 8/157

Conducting laboratory and location: —

Date of study initiation:

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle: 10 cm² oxybutynin — GMP transdermal patch.

Methods (unique aspects): two patches were used

Dosing:

Species/strain: Hartley-derived albino Guinea Pigs

#/sex/group or time point (main study): 14 males

Satellite groups used for toxicokinetics or recovery:

Age: young adults

Weight: 320-457 g

Doses in administered units: 2 10² cm patches

Route, form, volume, and infusion rate:

Observations and times:

Clinical signs:

Body weights:

Food consumption:
 Ophthalmoscopy:
 EKG:
 Hematology:
 Clinical chemistry:
 Urinalysis:
 Gross pathology:
 Organs weighed:
 Histopathology:
 Toxicokinetics:
 Other:

**APPEARS THIS WAY
 ON ORIGINAL**

Results:

Mortality: none
 Clinical signs:
 Body weights:
 Food consumption:
 Ophthalmoscopy:
 Electrocardiography:
 Hematology:
 Clinical chemistry:
 Urinalysis:
 Organ weights:
 Gross pathology:
 Histopathology:
 Toxicokinetics:

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 ON ORIGINAL**

Summary of individual study findings:

Toxicology summary: Ten male guinea pigs in each gp were dermally exposed to one 10 cm² GMP transdermal patch (A active or B placebo) or 0.5 ml of the positive control (0.3% dinitrochlorobenzene in acetone) for each of nine induction applications (three times/wk for 3 wks). Each application of the test or positive control article was applied to a site on the shaved area of the animals. The sites were rotated during the study. The positive control was applied by means of a 1x1 inch gauze patch, which was stabilized with a strip of hypoallergenic tape. An occlusive barrier consisting of a rubber patch was applied to the test and control sites and secured with — around the back and abdomen. After 6 hrs, all wrappings were removed.

Approximately 24 and 48 hrs following each induction application, the skin was scored for erythema and edema using the Draize scoring method.

Induction phase:

Seventeen days after the last induction dose was applied, guinea pigs from the test article and DNCB induction/challenge gps, and corresponding challenge irritation control gps were clipped and shaved along each side of the dorsal midline.

The following day, the appropriate patch (A or B) or 0.5 ml of 0.2% DNCB in acetone was applied to the naïve shaved site on each guinea pig in the induction/challenge and corresponding challenge irritation control gps. The patches and positive control were applied as previously described. After 6 hrs of exposure, the patches were removed.

Approximately 24, 48 and 72 hrs following the challenge application, the skin was scored for erythema and edema using the Draize scoring method.

Results:

At the time of the challenge exposure for GMP Transdermal Patch A, none of the animals in the induction/challenge gp exhibited dermal responses at the 24, 48 and 72 hr scoring periods. Two animals in the naïve challenge irritation control gp exhibited a score of 1 erythema at the 24 hr period. At the 48 and 72 hr periods, all animals were free of dermal irritation.

Four animals in the patch B induction/challenge gp exhibited a score of 1 erythema at the 24 hr period and one animal had a 1 score for edema as well. No dermal irritation was seen at 48 or 72 hrs. Three animals in the naïve challenge irritation control gp had dermal responses (2 had a score of 2 erythema and one had a score of 1 erythema) at 24 hrs. One animal had a score of 1 erythema at 48 hrs and there was no dermal irritation at 72 hrs.

Under the conditions of the test GMP Transdermal Patches A and B did not produce delayed contact sensitization. The positive control DNCB is a delayed contact sensitizer.

Toxicology conclusions:

Histopathology Inventory for NDA #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				

Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
 *, organ weight obtained

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GENETIC TOXICOLOGY:

Summaries of Japanese studies were submitted. Reversion tests using bacteria, chromosomal aberration tests using cultured mammalian cells and the single administration micronucleus test using mice were negative.

Study title:

Key findings:

Study no:

Study type (if not reflected in title):

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA reports: yes () no ()

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle:

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Methods:

Strains/species/cell line:

Dose selection criteria:

 Basis of dose selection:

 Range finding studies:

Test agent stability:

Metabolic activation system:

Controls:

 Vehicle:

 Negative controls:

 Positive controls:

 Comments:

Exposure conditions:

 Incubation and sampling times:

 Doses used in definitive study:

 Study design:

Analysis:

 No. of replicates:

 Counting method:

Criteria for positive results:

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Summary of individual study findings:

 Study validity:

 Study outcome:

Genetic toxicology summary:

Genetic toxicology conclusions:

Labeling recommendations:

CARCINOGENICITY:

None reviewed

Study title:

Key study findings:

Study number:

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA report: yes () no ()

Drug, lot #, and % purity:

CAC concurrence:

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Study Type (2 yr bioassay, alternative model etc.):

Species strain:

Number/sex/group; age at start of study:

Animal housing:

Formulation/vehicle:

Drug stability/homogeneity:

Methods:

Doses:

Basis of dose selection:

Restriction paradigm for dietary restriction studies:

Route of administration:

Frequency of drug administration:

Dual controls employed:

Interim sacrifices:

Satellite PK or special study group(s):

Deviations from original study protocol:

Statistical methods:

Observations and times:

Clinical signs:

Body weights:

Food consumption:

Hematology:

Clinical chemistry:

Organ weights:

Gross pathology:

Histopathology:

Toxicokinetics:

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Results:

Mortality:

Clinical signs:

Body weights:

Food consumption:

Hematology:

Clinical chemistry:

Organ weights:

Gross pathology:
Histopathology:
 Non-neoplastic:
 Neoplastic:
Toxicokinetics:

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Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:
Evaluation of tumor findings:

Carcinogenicity summary:

Carcinogenicity conclusions:

Recommendations for further analysis:

Labeling Recommendations: Labeling is satisfactory from the standpoint of Pharmacology.

Addendum/appendix listing:

Dose-ranging study report:
CAC report:
Alternative study protocols and CAC report:
Sponsor's incidence of histopathology findings:
List of organs and tissues examined:
Body weight changes versus dose level:
 Group body weight summary:
 Individual data listing:

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REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Summaries of Japanese studies were submitted. The effect of oxybutynin administered sc on embryo and fetal genesis was examined in rats and rabbits. At doses having maternal pharmacological and inhibition of weight gain, there were no adverse effects on maintenance of pregnancy or embryo and fetal genesis in rats or rabbits.

Study title:

Key study findings:

Study no.:

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA reports: yes () no ()

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle:

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Methods:

Species strain:

Doses employed:

Route of administration:

Study design:

Number sex/group:

Parameters and endpoints evaluated:

Results:

Mortality:

Clinical signs:

Body weight:

Food consumption:

Toxicokinetics:

For fertility studies:

In-life observations:

Terminal and necroscopic evaluations:

OR

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For embryofetal development studies:

In-life observations:

Terminal and necroscopic evaluations:

Dams:

Offspring:

OR

For peri-postnatal development studies:

In-life observations:

Dams:
Offspring:

Terminal and necroscopic evaluations:

Dams:
Offspring:

Summary of individual study findings:

Reproductive and developmental toxicology summary:

Reproductive and developmental toxicology conclusions:

Labeling recommendations:

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SPECIAL TOXICOLOGY STUDIES:

None reviewed

Study title:

Key study findings:

Study no:

Volume #, and page #:

Conducting laboratory and location:

Date of study initiation:

GLP compliance:

QA reports: yes () no ():

Drug, lot #, radiolabel, and % purity:

Formulation/vehicle:

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Methods:

Dosing:

Observations and times:

Results:

Summary of individual study findings:

Conclusions:

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Reviewer: _____

NDA No. _____

ADDENDUM TO REVIEW:
(if necessary)

APPENDIX/ATTACHMENTS:

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/s/

Alexander W. Jordan
2/20/02 02:37:26 PM
PHARMACOLOGIST