

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-228

ENVIRONMENTAL ASSESSMENT and/or FONSI

PART IV. ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT CLAIM FOR CATEGORICAL EXCLUSION

As cited at 21 CFR 25.15(d), an environmental assessment (EA) is not required if it is stated that the action requested qualifies for a categorical exclusion and, to the applicant's knowledge, no extraordinary circumstances exist.

Pharmacia & Upjohn Company's NDAs for Tolterodine Tartrate — Release Capsules and DETROL™ Tablets (Tolterodine Tartrate, PNU-200583E) qualify for a categorical exclusion based on Sec 25.31(b) wherein the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). A calculation of the expected introduction concentration (EIC) is provided below:

EXPECTED INTRODUCTION CONCENTRATION (EIC)

The fifth-year production estimate of tolterodine tartrate for the U.S. market is projected to be

Based on the equation for the theoretical maximum expected introduction concentration (EIC), the fifth-year production scenario is projected in the following equation:

EIC-aquatic (ppb)

$$= \frac{A \times B \times C \times D}{\dots}$$

where:

- A = kg/year produced for direct use (as active moiety)
- B = 1/liters per day entering POTWs*
- C = year/365 days
- D =

* 1.214×10^{11} liters per day entering publicly owned treatment works (POTWs).
(Source: 1996 Needs Survey, Report to Congress).

Utilizing the fifth-year production forecast for the drug substance of _____
environmental concentration of tolterodine tartrate that could be achieved is _____

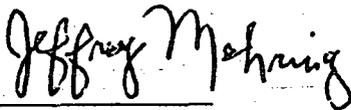
This concentration assumes complete and instantaneous release of the entire year's production, with no degradation.

EXTRAORDINARY CIRCUMSTANCES

To P&U's knowledge, no extraordinary circumstances, as specified in 21 CFR 25.21, exist in connection with action on this filing.

CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.



Jeffrey S. Mehring, Manager
Environment & Safety
Science & Data Management
(telephone 616/833-4746)

27 SEPT 99

Date

APPEARS THIS WAY
ON ORIGINAL

NDA 21-228
Tolterodine extended release capsules
- Pharmacia & Upjohn Company

Micro (validation of sterilization) review(s) and memoranda

Not applicable for this submission.

**APPEARS THIS WAY
ON ORIGINAL**

DO RECOMMENDATION 25-OCT-2000

ACCEPTABLE SEASTHAM
INSPECTION

AN ON-SITE PRE-APPROVAL INSPECTION WAS PERFORMED 10/17-19/00. NO
OBJECTIONABLE CONDITIONS WERE NOTED AND FIRM IS CAPABLE OF MANUFACTURING AND
TESTING THE PRODUCT.

OC RECOMMENDATION 30-OCT-2000

ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

Establishment: _____

DMF No: _____

AADA: _____

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL

OAI Status: NONE

Estab. Comment: ALTERNATE TESTING SITE FOR FULL COMPLIANCE

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-OCT-2000				RHEEM
OC RECOMMENDATION	17-OCT-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: _____

DMF No: _____

AADA: _____

Responsibilities: _____

Profile: CSN

OAI Status: NONE

Estab. Comment: _____

By M. ORTWERTH ()

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
SUBMITTED TO DO	05-APR-2000	GMP			EGASM
ASSIGNED INSPECTION	07-APR-2000	GMP			EGASM
INSPECTION SCHEDULED	16-AUG-2000		26-SEP-2000		IRIVERA
INSPECTION PERFORMED	12-OCT-2000		27-SEP-2000		EGASM
DO RECOMMENDATION	07-DEC-2000			ACCEPTABLE	EGASM
OC RECOMMENDATION	07-DEC-2000			INSPECTION ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 2650013

PHARMACIA AND UPJOHN CARIBE INC
HIGHWAY 2 KM 60.0
BARCELONETA/ARECIBO, PR 00617

DMF No: _____

AADA: _____

Responsibilities: DRUG SUBSTANCE MANUFACTURER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE
 Estab. Comment: MANUFACTURE (STEP 4 AND MILLING), QUALITY CONTROL, RELEASE, AND STABILITY TESTING OF TOLTERODINE L-TARTRATE B-PROCESSING DRUG SUBSTANCE (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
OC RECOMMENDATION	05-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 1810189

PHARMACIA AND UPJOHN CO
7000 PORTAGE ROAD
KALAMAZOO, MI 49001

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: CSN OAI Status: NONE
 Estab. Comment: DS OPERATIONS: MANUFACTURE (STEPS 1-3, ALTERNATE FOR STEP 4), QUALITY CONTROL, RELEASE, AND STABILITY TESTING OF TOLTERODINE L-TARTRATE B-PROCESS DRUG SUBSTANCE.
 DP OPERATIONS: PRIMARY PACKAGING, LABELING, QUALITY CONTROL, AND FINAL RELEASE OF THE DRUG PRODUCT. ALTERNATE FOR CAPSULE RELEASE AND STABILITY TESTING. (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
OC RECOMMENDATION	05-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-APR-2000				ORTWERTHM
OC RECOMMENDATION	07-APR-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 9610190

PHARMACIA AND UPJOHN SPA
MARINO DEL TRONTO, ASCOLI PICENO, IT

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: QUALITY CONTROL, RELEASE, STORAGE, AND STABILITY TESTING OF TOLTERODINE L-TARTRATE A-PROCESS DRUG SUBSTANCE. (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
SUBMITTED TO DO	05-APR-2000	10D			EGASM

ASSIGNED INSPECTION '07-APR-2000 GMP			EGASM
INSPECTION SCHEDULED 12-SEP-2000	13-OCT-2000		IRIVERA
INSPECTION PERFORMED 16-OCT-2000	13-OCT-2000		EGASM
DO RECOMMENDATION 07-DEC-2000		ACCEPTABLE	EGASM
		INSPECTION	
OC RECOMMENDATION 07-DEC-2000		ACCEPTABLE	EGASM
		DISTRICT RECOMMENDATION	

**APPEARS THIS WAY
ON ORIGINAL**