CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-771

CHEMISTRY REVIEW(S)

Dunson

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580

JAN 14 1998

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-771 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 09-JAN-98 **REVISED:** 14-JAN-1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA N-000	24-MAR-1997	26-MAR-1997	02-APR-1997
BC	29-AUG-1997	02-SEP-1997	03-SEP-1997
BC	18-NOV-1997	19-NOV-1997	19-NOV-1997
BC	18-NOV-1997	19-NOV-1997	19-NOV-1997
BC	31-DEC-1997	02-JAN-1998	07-JAN-1998

NAME & ADDRESS OF APPLICANT:

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME

Proprietary: Detrusitol™ tablets
Nonproprietary/USAN: Tolteridine tablets
Code Name/#:
Chem.Type/Ther.Class: 1S

PATENT STATUS: U.S. Patent # 5,382,600 exp. 2012

PHARMACOL.CATEGORY/INDICATION:

Treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms

DOSAGE FORM: tablet

STRENGTHS: 1 mg, 2 mg

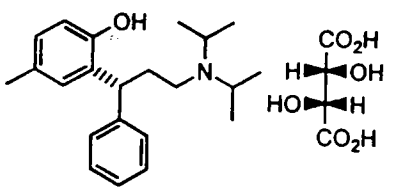
ROUTE OF ADMINISTRATION: oral

DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

R-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

$C_{26}H_{37}NO_7$



Tolterodine L-(+)-tartrate

M.W. = 475.58

SUPPORTING DOCUMENTS:

DMF #	Holder	Item

CONSULTS:

The proprietary name originally proposed for the drug product was Detrusitol. This name was submitted to the Labeling and Nomenclature Committee (LNC) on April 24, 1997 which noted one look-alike/sound-alike conflict to the proposed proprietary name, DETRUSITOL: DETUSSIN. Since Detussin is an OTC cough preparation, the Committee felt that there is a low potential for confusion. The LNC indicated that it found no misleading aspects with Detrusitol and stated that it had no reason to find the proposed name unacceptable on August 18, 1997. The firm submitted a request to evaluate two alternative names for the drug product on November 18, 1997. The two names, Detsel and Detrol, were submitted to the LNC on November 19, 1997. The LNC indicated that both names were acceptable on December 1, 1997.

An EER was submitted on May 9, 1997 and all manufacturing sites were found acceptable as of January 7, 1998.

REMARKS/COMMENTS:

This NDA is for an antimuscarinic drug for the treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms. Tolterodine L-tartrate is a New Molecular Entity.

The following amendments related to Chemistry, Manufacturing, and Controls have been submitted by the sponsor:

- August 29, 1997: Withdrew Environmental Assessment, requested Categorical Exemption
- November 18, 1997: Requested evaluation of the proprietary names Detsel and Detrol
- November 18, 1997: Content uniformity data for recent batches
- December 31, 1997: Recent drug product batches placed on stability

CONCLUSIONS & RECOMMENDATIONS:

The NDA may be approved from a chemistry standpoint provided that the firm adequately addresses the following issues:

- The firm should modify the drug substance specification to include a limit test for This test is currently performed as an in-process control.

- The firm should tighten the drug substance impurities specifications in accord with the low levels of impurities seen in the development batches and on stability.

- A deficiency letter has been sent to the in regard to their DMF for for blisters due to material in the DMF being in

- The sponsor needs to clarify whether a cap liner or innerseal is used in packaging the drug product and, if so, to describe the nature and source of the materials.

- The immediate container and carton labels are deficient because of the separation that created between the established and proprietary names by placing the latter in reverse print and surrounding it with heavy black bars.

- The firm needs to submit labeling with their choice of proprietary name from Detrusitol, Detsel and Detrol.

cc:
Orig. NDA 20-771
HFD-580/Division File
HFD-580/Chemist/Seevers
HFD-820/Division Director/Gibbs
HFD-820/Dep. Div. Director/Koepke
HFD-580/CSO/Dunson
R/D Init by: Rhee 1/14/98

1/14/98 /S/
Robert H. Seevers, Chemist

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DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-771 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 06-FEB-98 **REVISED:** 09-FEB-1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA N-000	24-MAR-1997	26-MAR-1997	02-APR-1997
BL	27-JAN-1998	28-JAN-1998	28-JAN-1998

NAME & ADDRESS OF APPLICANT:

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME

Proprietary: Detrol™ tablets
Nonproprietary/USAN: Tolteridine tablets
Code Name/#:
Chem.Type/Ther.Class: 1S

PATENT STATUS: U.S. Patent # 5,382,600 exp. 2012

PHARMACOL.CATEGORY/INDICATION:

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DOSAGE FORM: tablet

STRENGTHS: 1 mg, 2 mg

ROUTE OF ADMINISTRATION: oral

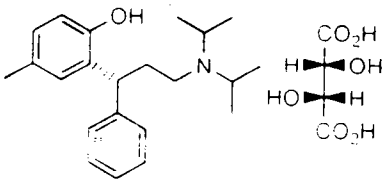
DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

R-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

$C_{32}H_{48}N_2O_{12}$

MW = 652.74



Tolteridine L-(+)-tartrate

SUPPORTING DOCUMENTS:

DMF #	Holder	Item

CONSULTS:

The proprietary name originally proposed for the drug product was Detrusitol. This name was submitted to the Labeling and Nomenclature Committee (LNC) on April 24, 1997 which noted one look-alike/sound-alike conflict to the proposed proprietary name, DETRUSITOL: DETUSSIN. Since Detussin is an OTC cough preparation, the Committee felt that there is a low potential for confusion. The LNC indicated that it found no misleading aspects with Detrusitol and stated that it had no reason to find the proposed name unacceptable on August 18, 1997. The firm submitted a request to evaluate two alternative names for the drug product on November 18, 1997. The two names, Detsel and Detrol, were submitted to the LNC on November 19, 1997. The LNC indicated that both names were acceptable on December 1, 1997.

An EER was submitted on May 9, 1997 and all manufacturing sites were found acceptable as of January 7, 1998.

REMARKS/COMMENTS:

This NDA is for an antimuscarinic drug for the treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms. Tolterodine L-tartrate is a New Molecular Entity. The present review is of the sponsor's response to chemistry deficiencies identified in the initial review and communicated in a letter to the sponsor dated January 16, 1998.

CONCLUSIONS & RECOMMENDATIONS:

The sponsor has provided satisfactory responses to each of the issues raised by the first chemistry review with the exception of the label. The NDA may be approved from a chemistry standpoint when the sponsor has appropriately modified the label to remove the stick figure logo that has been placed next to the trade name.

Acceptable label submitted
2/25/98
N.D.
3/11/98

cc:
Orig. NDA 20-771
HFD-580/Division File
HFD-580/Chemist Seevers
HFD-820/Division Director Gibbs
HFD-820/Dep. Div. Director Koepke
HFD-580/CSO Dunson
R.D Init by: Rhee

Robert H. Seevers, Chemist

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-771 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 03-MAR-1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA N-000	24-MAR-1997	26-MAR-1997	02-APR-1997
BL	24-FEB-1998	25-FEB-1998	02-MAR-1998
BL	25-FEB-1998	26-FEB-1998	02-MAR-1998

NAME & ADDRESS OF APPLICANT:

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME

Proprietary: Detrol™ tablets
Nonproprietary/USAN: Tolteridine tablets
Code Name/#:
Chem.Type/Ther.Class: 1S

PATENT STATUS: U.S. Patent # 5,382,600 exp. 2012

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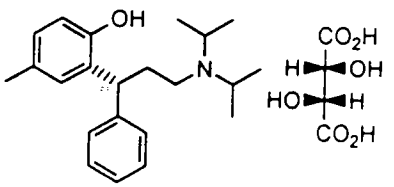

Tolterodine L-(+)-tartrate

SUPPORTING DOCUMENTS: None

CONSULTS:

The proprietary name originally proposed for the drug product was Detrusitol. This name was submitted to the Labeling and Nomenclature Committee (LNC) on April 24, 1997 which noted one look-alike/sound-alike conflict to the proposed proprietary name, DETRUSITOL: DETUSSIN. Since Detussin is an OTC cough preparation, the Committee felt that there is a low potential for confusion. The LNC indicated that it found no misleading aspects with Detrusitol and stated that it had no reason to find the proposed name unacceptable on August 18, 1997. The firm submitted a request to evaluate two alternative names for the drug product on November 18, 1997. The two names, Detsel and Detrol, were submitted to the LNC on November 19, 1997. The LNC indicated that both names were acceptable on December 1, 1997.

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REMARKS/COMMENTS:

This NDA is for an antimuscarinic drug for the treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms. Tolterodine L-tartrate is a New Molecular Entity. The present review is of the sponsor's response to labeling concerns. The February 24 submission covers the package insert and the February 25 submission covers the non-insert labeling.

CONCLUSIONS & RECOMMENDATIONS:

The sponsor has satisfactorily addressed the labeling concerns. The NDA may be approved from a chemistry standpoint.

cc:
Orig. NDA 20-771
HFD-580/Division File
HFD-580/Chemist/Seevers
HFD-820/Division Director/Gibbs
HFD-820/Dep. Div. Director/Koepke
HFD-580/CSO/Dunson
R/D Init by: Rhee 3/5/98

/S/

Robert H. Seevers, Chemist