

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**CHEMISTRY REVIEW**

CHEMIST REVIEW #1  
OF SUPPLEMENT

1. ORGANIZATION HFD-580
2. NDA NUMBER: 20-771
3. SUPPLEMENT NUMBERS/DATES: SE8-004  
Letterdate: 22-DEC-1999  
Stampdate: 23-DEC-1999
4. AMENDMENTS/REPORTS/DATES:  
Letterdate:  
Stampdate:
5. RECEIVED BY CHEMIST: 10-MAR-2000

6. APPLICANT NAME AND ADDRESS:

Pharmacia & Upjohn  
7000 Portage Road  
Kalamzoo, MI 49001

7. NAME OF DRUG: Detrol™ (tolterodine tartrate) Tablets

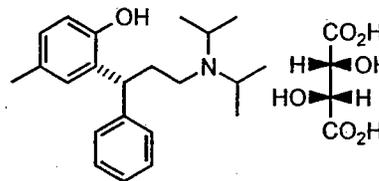
8. NONPROPRIETARY NAME: Tolterodine Tartrate

9. CHEMICAL NAME/STRUCTURE:

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

$C_{26}H_{37}NO_7$

M.W. = 475.58



Tolterodine L-(+)-tartrate

10. DOSAGE FORM(S): Tablet

11. POTENCY: 1mg and 2 mg

12. PHARMACOLOGICAL CATEGORY: antimuscarinic

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

13. HOW DISPENSED: Rx

14. RECORDS & REPORTS CURRENT: Yes

15. RELATED IND/NDA/DMF:

16. SUPPLEMENT PROVIDES FOR: This efficacy supplement provides for changes to product labeling in the "Description" section of the package insert.

17. COMMENTS

The changes to the "Description" section of the package insert labeling includes addition of the following statement:

"The pKa value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3."

The "How Supplied" section of the package insert labeling contains an outdated room temperature storage statement.

18. CONCLUSIONS AND RECOMMENDATIONS:

This supplement can be APPROVED from a chemistry, manufacturing and controls perspective.

19. REVIEWER NAME  
Michael Ortwerth, Ph.D.  
Review Chemist

SIGNATURE

DATE COMPLETED

27-MAR-2000

cc: Original: NDA # 20-771  
HFD-580/Division File  
HFD-580/CSO/EFarinas  
HFD-580/Chemist/MRhee/MOrtwerth  
INIT: MJ Rhee

filename: N20771SuppSE8004Rev1.do.

**CHEMIST REVIEW  
OF SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-771/SE8-004
3. **SUPPLEMENT NUMBERS/DATES:**  
    **Letterdate:** 22-DEC-1999  
    **Stampdate:** 23-DEC-1999
4. **AMENDMENTS/REPORTS/DATES:**  
    **Letterdate:**  
    **Stampdate:**
5. **RECEIVED BY CHEMIST:** 11-AUG-2000

**6. APPLICANT NAME AND ADDRESS:**

Pharmacia & Upjohn Co.  
7000 Portage Road  
Kalamazoo, MI 49001

**7. NAME OF DRUG:**

Detrol

**8. NONPROPRIETARY NAME:**

Tolterodine tartrate tablets

**9. CHEMICAL NAME/STRUCTURE:**

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

see USP Dictionary of Drug Names for structure

**10. DOSAGE FORM(S):**

Tablets

**11. POTENCY:**

1 mg, 2 mg

**12. PHARMACOLOGICAL CATEGORY:**

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

**13. HOW DISPENSED:**

RX

**14. RECORDS & REPORTS CURRENT:**

Yes

**15. RELATED IND/NDA/DMF:**

none

**16. SUPPLEMENT PROVIDES FOR:**

Efficacy supplement to revise the clinical study section of the package insert.

**17. COMMENTS**

The only CMC issue in this supplement concerns a revision in the Description section of the package insert. The sponsor proposes to delete the following sentence \_\_\_\_\_

and replace it with the following sentences: "The pKa value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3." Based on the physical properties data provided in the original NDA, the revised labeling is acceptable.

Review of the package insert reveals that the storage statement in the How Supplied section should be revised from \_\_\_\_\_

\_\_\_\_\_ "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]". This comment has been conveyed to the sponsor, but the sponsor has not responded.

**18. CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC point of view, this Supplement may be approved pending satisfactory resolution of the above labeling issue.

**19. REVIEWER NAME**

David T. Lin, Ph.D.  
Review Chemist

**SIGNATURE**

\_\_\_\_\_

**DATE COMPLETED**

16-OCT-2000

10/16/00

cc: Original: NDA 20-771/SE8-004  
HFD-580/Division File  
HFD-580/EFarinas  
HFD-580/MRhee/DLin

INIT by MJ Rhee

\_\_\_\_\_

Filename: S20771.004 (doc)

**CHEMIST REVIEW #2  
OF SUPPLEMENT**

- 1. ORGANIZATION:** DRUDP HFD-580
- 2. NDA NUMBER:** 20-771/SE8-004
- 3. SUPPLEMENT NUMBERS/DATES:**  
**Letterdate:** 22-DEC-1999  
**Stampdate:** 23-DEC-1999
- 4. AMENDMENTS/REPORTS/DATES:**  
**Letterdate:** 26-OCT-2000  
**Stampdate:** 27-OCT-2000
- 5. RECEIVED BY CHEMIST:** 11-AUG-2000

**6. APPLICANT NAME AND ADDRESS:**

Pharmacia & Upjohn Co.  
7000 Portage Road  
Kalamazoo, MI 49001

**7. NAME OF DRUG:**

Detrol

**8. NONPROPRIETARY NAME:**

Tolterodine tartrate tablets

**9. CHEMICAL NAME/STRUCTURE:**

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

see USP Dictionary of Drug Names for structure

**10. DOSAGE FORM(S):**

Tablets

**11. POTENCY:**

1 mg, 2 mg

**12. PHARMACOLOGICAL CATEGORY:**

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

**13. HOW DISPENSED:**

RX

**14. RECORDS & REPORTS CURRENT:**

Yes

**15. RELATED IND/NDA/DMF:**

none

**16. SUPPLEMENT PROVIDES FOR:**

Efficacy supplement to revise the clinical study section of the package insert.

**17. COMMENTS**

The October 26, 2000 amendment is a response to the Division's October 23, 2000 approvable letter. The sponsor has revised the storage statement as requested. See Chemistry Review #1 dated October 16, 2000 for further details.

**All relevant CMC issues have been adequately addressed in the latest label.**

**18. CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC point of view, this Supplement may be approved.

**19. REVIEWER NAME**

David T. Lin, Ph.D.  
Review Chemist

**SIGNATURE**

**DATE COMPLETED**

26-MAR-2001

**cc: Original: NDA 20-771/SE8-004**

**HFD-580/Division File**

**HFD-580/EFarinas**

**HFD-580/MRhee/DLin**

**INIT by MJ Rhee**

Filename: S20771AC.004 (doc)

/s/

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David T. Lin  
3/26/01 02:00:36 PM  
CHEMIST

Labeling supplement: revised storage statement

Moo-Jhong Rhee  
3/26/01 04:53:22 PM  
CHEMIST  
I concur