CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-030

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 14, 2008
To:	Scott Monroe, M.D., Director **Division of Reproductive & Urologic Products**
Through:	Jodi Duckhorn, M.A. Team Leader **Patient Labeling and Education Team** **Division of Risk Management**
From:	Nancy Carothers, BA, RN Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management**
Subject:	Review of Patient Labeling for TOVIAZ™ (Patient Package Insert), #2
Drug Name(s):	TOVIAZ™ (fesoterodine fumarate, extended release tablets)
Application Type/Number:	NDA 22-030
Applicant/sponsor:	Pfizer
OSE RCM #:	2008-810

RESPONSE TO SPONSOR'S REVISIONS TO THE PPI:

Please see our response the sponsor's revision of the TOVIAZ PPI:

1. If the sponsor [redacted] we recommend the term "doctor." One term should be used consistently throughout the PPI. We recommend against the term "healthcare professional" as it is not generally understood.
2. We defer to the Review Division on the question of whether TOVIAZ inhibits or induces enzymes involved in the metabolism of other drugs.
3. We recommend retaining the bullet, '[redacted] [doctor] may give you a lower dose if you have certain medical conditions such as severe kidney problems." The PI states in three sections (Phamacokinetics in Special Populations, Dosage and Administration, and Precautions) that TOVIAZ is not recommended for patients with severe renal insufficiency at doses higher than 4 mg. This bullet provides additional safety information concerning the patient's medical condition (severe renal insufficiency) and the recommended dosing of TOVIAZ. It is important for these patients to understand clearly that a higher dose is not recommended, especially if their renal problems change from less serious to more serious during their course of treatment with TOVIAZ.
4. [redacted] b(4)
5. We agree with listing "constipation" as one of the most common side effects.
6. [redacted] b(4)
7. The statement, "Safely throw away TOVIAZ that is out of date or no longer needed" [redacted] Again, we generally recommend following the Medication Guide regulations as much as possible for consistency across all patient labeling.

MATERIAL REVIEWED FOR THIS RESPONSE:

- **TOVIAZ™** PI submitted by the Sponsor on May 1, 2008 and further revised by the reviewing division on September 4, 2008
- **TOVIAZ™** PPI submitted by the Sponsor on May 1, 2008 and further revised by the reviewing division on September 9, 2008

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/s/

Nancy B Carothers
10/14/2008 02:36:42 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
10/14/2008 03:05:40 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
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Maternal Health Team Review

Date: September 8, 2008 **Date Consulted:** June 27, 2008

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Tammie Brent, RN, MSN
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Reproductive and Urologic Products (DRUP)

Drug: Toviaz (fesoterodine fumarate) tablets; NDA 22-030

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Toviaz labeling.

Consult Question: This request is for a labeling consult for NDA 22-030. Please review the Pregnancy and Nursing Mothers subsections of labeling.

INTRODUCTION

On January 25, 2007, the Division of Reproductive and Urologic Products (DRUP) issued an approvable letter to Schwarz Bioscience, a manufacturer for Pfizer Global Pharmaceuticals, for their new drug application (NDA) 22-030 for Toviaz (fesoterodine fumarate). On May 2, 2008, Pfizer Global Pharmaceuticals submitted a complete response to the approvable letter for NDA 22-030 to DRUP. The sponsors proposed indication for Toviaz is for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

On June 27, 2008, DRUP consulted the Maternal Health Team (MHT) to review and revise the pregnancy and nursing mothers section of the Toviaz package insert. This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Toviaz labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Toviaz labeling. The revisions are provided in both non-PLR format and in PLR format.

SUMBMITTED MATERIAL
Sponsors Proposed Pregnancy and Nursing Mothers Labeling

Pregnancy
Pregnancy Category C

b(4)

with 75 mg/kg/day (9 to 27 times the expected exposure at the

b(4)

Nursing Mothers

b(4)

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsors' proposed labeling. The recommendations are provided in non-PLR format and in PLR format. Additionally, MHT requested the pharmacology/toxicology team calculate the correct multiple of human exposure based on AUC at MRHD for the mouse dose of 30 mg/kg/day (see attached label for comment). Appendix A of this review provides a track changes version of labeling that highlights all changes made.

1) Non-PLR Format:

Pregnancy
Pregnancy Category C

b(4)

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

1 other Reviews

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Toviaz is provided on pages 3-5 of this review. Appendix A of this review also provides a track changes version of labeling.

Appendix A –
Track Changes Version of Labeling

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

2 Other Review

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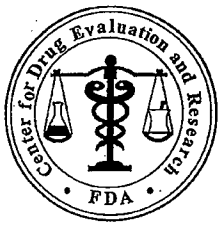
/s/

Tammie Brent-Steele
9/12/2008 01:53:41 PM
CSO

Chardae Araojo
9/15/2008 09:02:53 AM
CSO

Karen Feibus
9/16/2008 05:01:41 PM
MEDICAL OFFICER

Lisa Mathis
9/18/2008 09:07:57 PM
MEDICAL OFFICER



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	**September 10, 2008**
To:	**Scott Monroe, M.D., Director** **Division of Reproductive & Urologic Products**
Through:	**Jodi Duckhorn, M.A. Team Leader** **Patient Labeling and Education Team** **Division of Risk Management**
From:	**Nancy Carothers, BA, RN** **Patient Product Information Specialist** **Patient Labeling and Education Team** **Division of Risk Management**
Subject:	**Review of Patient Labeling for TOVIAZ™ (Patient Package Insert)**
Drug Name(s):	**TOVIAZ™ (fesoterodine fumarate, extended release tablets)**
Application Type/Number:	**NDA 22-030**
Applicant/sponsor:	**Pfizer**
OSE RCM #:	**2008-810**

1 INTRODUCTION

On May 1, 2008, the sponsor submitted a Complete Response, to FDA's "Approvable letter" sent to the sponsor on January 25, 2007. The Complete Response included revisions to the Professional Information (PI), Patient Package Insert (PPI), and packaging; along with clinical pharmacology and clinical study updates as requested by FDA. The PPI was updated from a version submitted with the original NDA on March 16, 2006. The revised PPI contains the new trade name, TOVIAZ, and other editorial changes, and is presented in the FDA recommended question-and-answer format.

The Division of Reproductive and Urologic Products requested that the Patient Labeling and Education Team review the Patient Package Insert (PPI) for this product. This review is written in response to that request.

2 MATERIAL REVIEWED

- **TOVIAZ™** PI submitted by the Sponsor on May 1, 2008 and further revised by the reviewing division on September 4, 2008
- **TOVIAZ™** PPI submitted by the Sponsor on May 1, 2008 and further revised by the reviewing division on September 9, 2008

3 DISCUSSION

The purpose of patient labeling is to enhance appropriate use of and to provide important risk information about medicines. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The PPI submitted by the sponsor has a Flesch Kinkaid grade level of 7.6, and a Flesch Reading Ease score of 59.1 %. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level).

In our review of the PPI, we have:

- simplified the wording and clarified concepts where possible,
- made the information in the PPI consistent with the PI,
- removed unnecessary and redundant information from the PPI,
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined, and italicized***.

We are providing to the review division a marked-up and clean copy of the revised PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

b(4)

- The PI says in the *Information for Patients* section that alcohol may enhance the drowsiness caused by anticholinergic agents, such as TOVIAZ.
- The Precautions, Drug-Drug Interactions, and Dosage and Administration sections of the PI, state that an interaction with potent CYP3A4 inhibitors may occur when using TOVIAZ doses greater than 4 mg daily. Patients should be told to tell their healthcare provider, specifically, if they are taking antibiotics or antifungal medicines. A patient's infectious condition may not be related to overactive bladder and, as a result, may not be apparent to the prescribing healthcare provider.
- In the *How should I take TOVIAZ?* section of the PPI, add information on taking a lower dose for patients with severe kidney problems, and instructions on what to do if a dose is missed or for an overdose.
- The activities for patients to avoid: 1) use of alcohol that can increase drowsiness, 2) a heated or warm environment that can cause heat prostration (due to decreased sweating), and blurred vision appear in the *Information for Patients* section of the PI These activities should be added to the section of the PPI.

b(4)

- Under the section on the possible side effects, we added the following information:
  Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

  This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse events on Labeling for Human Drug Products in Federal Register Vol. 73, No.2, p.402-404, 1/3/2008). Although not required for voluntary PPIs, like TOVIAZ, we recommend adding this language to all FDA-approved patient labeling for consistency.

- Patients should be advised on the safe disposal of their medicines and this should be added to the section, *How should I store TOVIAZ?* Some formulations cannot be thrown away and should not be flushed, according to the White House and EPA recommendations. This information should be added to the PI for consistency.
- The sponsor uses both the terms "doctor" ~~——————————————~~ ~~————————~~ We recommend that one term be used consistently throughout the PPI.

Please let us know if you have any questions.

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On Original

9 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

3 Other Reviews

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/s/

Nancy B Carothers
9/10/2008 04:21:59 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
9/10/2008 04:25:49 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Pre-decisional Agency Information

Date: July 25, 2008

From: Elaine Hu Cunningham, DDMAC
Aline Moukhtara, DDMAC

To: Celia Hayes, DRUDP

Re: Toviaz™ (fesoterodine fumarate) extended-release tablets
NDA 22-030

DDMAC comments are provided on draft PI, PPI, and carton labeling submitted by Pfizer on May 2, 2008 for Toviaz™ (fesoterodine fumarate) extended-release tablets.

DRAFT PI DATED APRIL 22, 2008:

DESCRIPTION

Fesoterodine is rapidly de-esterified to its active metabolite... (emphasis added)

The descriptor, "rapidly," is promotional in nature and may be used in promotional materials to imply superiority or overstate the efficacy of Toviaz compared to its competitors. Please consider deleting this descriptor to be consistent with competitors' labeling information.

CLINICAL PHARMACOLOGY

5 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4 other Review

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/s/

Elaine J. Hu
7/25/2008 03:31:19 PM
DDMAC REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 31, 2006

TO: Daniel Shames, M.D. Director
Division of Reproductive and Urologic Drug Products

VIA: Jean Makie, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products

FROM: Sharon R. Mills, B.S.N., R.N., C.C.R.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for TRADENAME (fesoterodine fumarate), NDA 22-030.

See the attached Patient Package Insert (PPI) for our recommended revisions to the proposed patient labeling for TRADENAME (fesoteridone fumarate) 4 mg and 8 mg extended-release tablets, NDA 22-030. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have simplified the wording where possible, made it consistent with the Professional Labeling (PI) and removed unnecessary information. We have also put this PPI in the patient-friendly format (specified in 21 CFR 208.20) that we are recommending for all FDA approved patient labeling, although this format is not required for voluntary PPIs. These recommended changes are consistent with research to improve risk communication to a lower literacy audience.

These revisions are based on proposed professional labeling (PI) submitted on March 17, 2006 for this new molecular entity. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. A PPI for TRADENAME (fesoterodine fumarate) is voluntary. Except where drug products are dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. According to the PI, TRADENAME (fesoterodine fumarate) will be supplied in bottles of 30 and 90 tablets. The sponsor should state their mechanism for intended distribution of the PPI to patients.
2. The sponsor uses the terms "doctor" [redacted] in the proposed PPI. The patient may be confused about who they should talk to. We recommend that you use one term consistently throughout the PPI. b(4)
3. Heat prostration is a possible adverse event that can occur in patients taking TRADENAME (fesoterodine femarate) and other OABs as well as other anticholinergic drugs. It is in the PI but is not reflected in the draft PPI submitted by the sponsor. We have added language t [redacted] Patients taking TRADENAME (fesoterodine fumarate) should be made aware that they may become overheated and why, as well as what action(s) to take. b(4)

Comments to the review division are ***bolded, underlined and italicized***. We are providing a marked-up and clean copy of the revised PPI attached to this memo as well as separate electronic word files.

Please call us if you have any questions.

8 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

5 Other Reviews

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/s/

Sharon Mills
7/31/2006 09:52:54 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
7/31/2006 05:53:51 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO: 22, Mailstop 4447)

DATE RECEIVED: May 15, 2006	**DESIRED COMPLETION DATE:** August 15, 2006	**OSE REVIEW #:** 05-0071-2
DOCUMENT DATE: March 17, 2006	**PDUFA DATE:** January 27, 2007	

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Products
HFD-580

THROUGH: Alina Mahmud, RPh., MS, Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda Wisniewski, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:
Fesoteridine Fumarate Extended-release Tablets
4 mg and 8 mg

NDA#: 22-030 (IND# 51,232)

NDA SPONSOR: Schwarz Pharma

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section II of this review to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO: 22 Mailstop 4447
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: May 25, 2006

NDA#: 22-030 (IND#: 51,232)

NAME OF DRUG: Fesoterodine Fumarate Extended-release Tablets
4 mg and 8 mg

NDA HOLDER: Schwarz Pharma

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Products (HFD-580) for a review of the proposed container labels, carton and insert labeling of Fesoteridine Fumarate Extended-release Tablets. DMETS reviewed the previously proposed proprietary name, ——, for IND# 51,232 in ODS Consult 05-0071 which was found acceptable by DMETS on November 18, 2005. Additionally, the sponsor submitted an alternate name, —— for evaluation. The Division of Drug Marketing, Advertising and Communications (DDMAC) did not recommend the use of the proprietary name, ——, from a promotional perspective because ——— The Division concurred with DDMAC. Thus, DMETS did not proceed with the safety review of the name ——. At this time, the sponsor has not submitted a proprietary name for this product. They have not decided if they want to proceed with —— or choose a different name. b(4)

PRODUCT INFORMATION

Fesoterodine Fumarate is a competitive muscarinic receptor antagonist and is indicated in the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. The recommended starting dose is 4 mg once daily and based on individual patient response, the dose may be increased to 8 mg once daily. It should be taken once daily with liquid and swallowed whole with or without food and should not be chewed, divided, or crushed. It will be supplied in 4 mg and 8 mg tablets and packaged in bottles of 30 and 90 tablets.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Fesoteridine Fumarate Extended-release Tablets, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1.

2. b(4)

3.

B. CONTAINER LABEL (30 count and 90 count)

1. See GENERAL COMMENTS.

2. Ensure that the 30-count and 90-count unit-of-use container has a child resistant closure to be in accordance with the Poison Prevention Act. We refer you to 16 CFR 1700.15 and 1700.15 for guidance.

C. CONTAINER LABEL (Professional Sample Blister, 7-count)

1. See GENERAL COMMENT A2.

2. b(4)

3.

4. b(4)

b(4)

Figure 1.

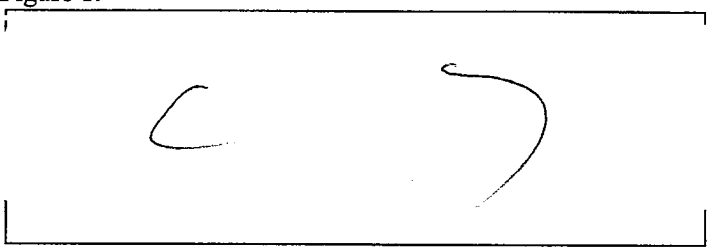
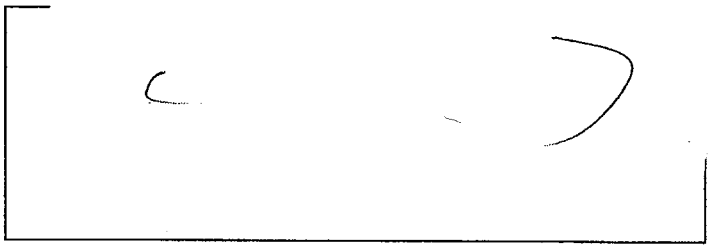


Figure 2.

b(4)



DMETS considers a configuration similar to that in Figure 1 acceptable. However, DMETS considers a configuration similar to that in Figure 2 above

D. CARTON LABELING (Professional Sample, One blister card)

1. See GENERAL COMMENTS.

2. Include a usual dose statement. See 21 CFR 201.55.

E. CARTON LABELING (Professional Sample Display, 7 x 7)

1. See GENERAL COMMENTS.

2.

b(4)

3. Include a usual dose statement. See 21 CFR 201.55

F. INSERT LABELING

Repeat Precautions Information for Patients at the end of the package insert labeling.

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/s/

Linda Wisniewski
7/18/2006 03:55:05 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
7/18/2006 03:56:30 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/18/2006 04:42:43 PM
DRUG SAFETY OFFICE REVIEWER