King, Jean

From: Jon.Villaume@us.sanofi.com
Sent: Thursday, June 12, 2003 7:23 PM
To: kingje@cder.fda.gov
Cc: GV-RDU@sanofi-synthelabo.com
Subject: NDA 21-287 Final professional package insert.



HIGHLIGHTED ALFUZOSIN mmsinfo.txt
JZOSIN FINAL I. PACKAGE INSI

Ms Jean King
FDA Reproductive Drugs Division

Attached is the final package insert containg all changes agreed to with you in our 12 June 2003 teleconference.

The first copy is a highlighted copy based on the version provided by FDA
on 12 June 2003. All changes from the 12 June 2003 FDA version are highlighted.
The second version is a clean version with all agreed-upon changes incorporated.

Jon Villaume

..ighlighted version (See attached file: HIGHLIGHTED ALFUZOSIN FINAL PACKAGE INSERT12 June 2003.doc)

Version without highlights(See attached file: ALFUZOSIN FINAL PACKAGE INSERT12 June 2003.doc)

17 pages redacted from this section of the approval package consisted of draft labeling

To Lisa Davis

From: Jon Villaume

1 pages redacted from this section of the approval package consisted of draft labeling

12 June 2003

Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: NDA 21-287
Alfuzosin HCl once daily for benign prostatic hyperplasia
Professional package insert
Amendment XX

Dear Dr. Shames:

We are providing a revised draft package insert dated 11 June 2003. The draft package insert dated 11 June 2003 contains wording agreed upon at our teleconference on 11 June with Dr. Griebel.

The 11 June 2003 draft also contains our proposal to describe the results of the study to assess the affect of alfuzosin on cardiac repolarization. To our understanding this is the only area of in the package insert, which remains unresolved.

On 10 June 2003 we provided a draft package insert dated 10 June 2003. The 10 June version is the basis for all changes in the draft dated 11 June 2003. All additions to the 10 June version are highlighted in red and all deletions are crossed through. We are providing two versions of the 11 June 2003 draft package insert, one with highlighting and one without highlighting.

Please contact me by phone at 610-889-6028 or facsimile at 610-889-6993 if you have any comments or questions concerning this correspondence.

Sincerely,

/s/

Jon E. Villaume, Ph.D.
Senior Director

17 pages redacted from this section of the approval package consisted of draft labeling

King, Jean

om: Jon.Villaume@us.sanofi.com
Sent: Thursday, June 12, 2003 7:28 PM
To: kingje@cder.fda.gov
Cc: GV-RDU@sanofi-synthelabo.com
Subject: NDA 21-287 clean PPI


ALFUZOSIN PATIENT INFC mmsinfo.txt

Jean

Here is a clean PPI that we agreed upon.

Jon

(See attached file: ALFUZOSIN FINAL PATIENT INFORMATION 12 June 2003.doc)

4 pages redacted from this section of the approval package consisted of draft labeling

King, Jean

.om: Jon.Villaume@us.sanofi.com
Sent: Thursday, June 12, 2003 3:08 PM
To: kingje@cder.fda.gov
Subject: NDA21-287 patient package insert


ALFUZOSIN
[PATIENT INFC


mmsinfo.txt

Jean,

Our comments on your draft of the PPI are highlighted.

Jon

(See attached file: ALFUZOSIN DRAFT PATIENT INFORMATION DRAFT 12 June 2003.doc)

5 pages redacted from this section of the approval package consisted of draft labeling

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: February 4, 2003	DUE DATE: June 1, 2003	ODS CONSULT #: 03-0059

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

THROUGH: Jean King
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:** Sanofi-Synthelabo Inc.
(Primary) (Secondary) (Alfuzosin Hydrochloride Extended Release Tablets) 10 mg **NDA#: 21-287**	

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names and to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, However, DMETS has no objections to the use of the proposed name, DMETS decision is considered tentative. We request submission of the container labels and labeling for review and comment. The name and its labels must be reviewed approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature of this document.

2. DDMAC does not recommend the use of the names from a promotional perspective for the following reasons: The name misleading and implies total relief of benign prostatic hyperplasia (BPH) symptoms, and the name is not acceptable because it is overly fanciful.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 11, 2003

NDA# 21-287

NAME OF DRUG: [redacted] (Primary) and [redacted] (Secondary)
(Alfuzosin Hydrochloride Extended Release Tablets)
10 mg

NDA HOLDER: Sanofi-Synthelabo Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), for an assessment of the proposed proprietary names, [redacted] and [redacted] regarding potential name confusion with other proprietary and/or established drug names. The sponsor previously submitted the proprietary names [redacted] (OPDRA Consult # 00-0191), which was not recommended for approval due to safety concerns, and Uroxatral (OPDRA Consult # 00-0093), which was recommended for approval. However, the sponsor no longer prefers this name, and submitted the two alternate names for consideration. Additionally, the sponsor has submitted additional information, including an independent analysis conducted by [redacted] to DMETS for review and comment. The container labels, carton labeling and package insert labeling for [redacted] and [redacted] were not submitted for review and comments.

PRODUCT INFORMATION

[redacted] is an extended release tablet that contains alfuzosin, a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsules, and prostatic urethra. [redacted] is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia. It is not indicated for the treatment of hypertension. [redacted] will be available as 10 mg tablets. The recommended dosage is one tablet daily, to be taken after the same meal each day.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or Look-alike to [redacted] and [redacted] to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study for each name, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names [redacted] and [redacted] Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with [redacted] Additionally, the Expert Panel identified two drug names that were thought to have potential for confusion with [redacted] These products are listed in table 1 and table 2 (see page 4), along with the usual dosage and available dosage forms.

2. DDMAC objects to the name [redacted] because it is misleading and implies total relief of benign prostatic hyperplasia (BPH) symptoms. Additionally, DDMAC stated that the name [redacted] is not acceptable, as it is overly fanciful.

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[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] Data provided by Thomson & Thomson's SEAGIS™ Online Service available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
[redacted]	**Alfuzosin Hydrochloride Extended Release Tablets 10 mg**	**Take one tablet daily after the same meal each day.**	
[redacted]	[redacted]		
Duricef (Rx)	Cefadroxil Capsules: 500 mg Tablets: 1 gram Suspension: 125 mg/5 mL, 250 mg/5 mL and 500 mg/5 mL	Urinary Tract Infection Uncomplicated: 1 or 2 grams per day in single or divided doses. Other: 2 grams per day in 2 divided doses. Skin and skin structure infections 1 gram per day in single or 2 divided doses. Pharyngitis and tonsillitis (caused by Group A beta-hemolytic streptococci) 1 gram per day in a single or 2 divided doses for 10 days.	**L/A
Aricept (Rx)	Donepezil Tablets 5 mg and 10 mg	Take 5 mg to 10 mg daily	**L/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
NOTE: This review contains proprietary and confidential information that should not be released to the public.

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
[redacted]	**Alfuzosin Hydrochloride Extended Release Tablets 10 mg**	**Take one tablet daily after the same meal each day.**	
Estring (Rx)	Estradiol Vaginal Ring 2 mg (Delivers 7.5 micrograms/24 hrs.)	Insert one ring high into vagina. Replace after 90 days.	**S/A
Amnesteem (Rx)	Isotretinoin Capsules, USP 10 mg, 20 mg, and 40 mg (Reference Listed Drug – Accutane)	0.5 mg/kg/day to 1 mg/kg/day divided into 2 doses for 15 to 20 weeks. Maximum dose is 2 mg/kg/day.	**S/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
NOTE: This review contains proprietary and confidential information that should not be released to the public.

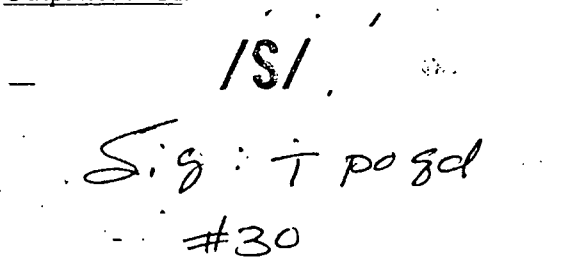
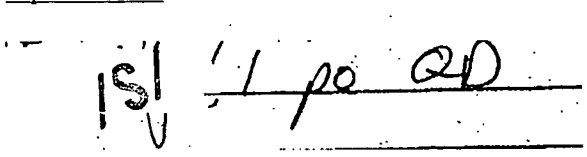
B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

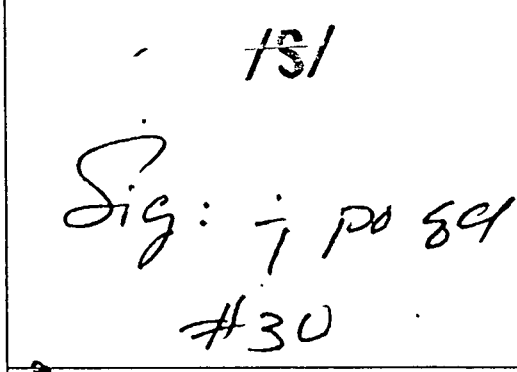
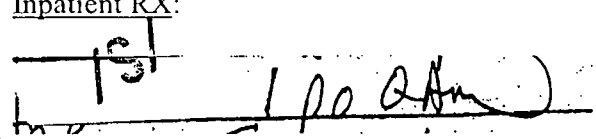
Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of [redacted] and [redacted] with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of

a combination of marketed and unapproved drug products and a prescription for [redacted] and [redacted] (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

[redacted]

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	[redacted] take one by mouth daily, dispense #30.
Inpatient RX: 	

[redacted]

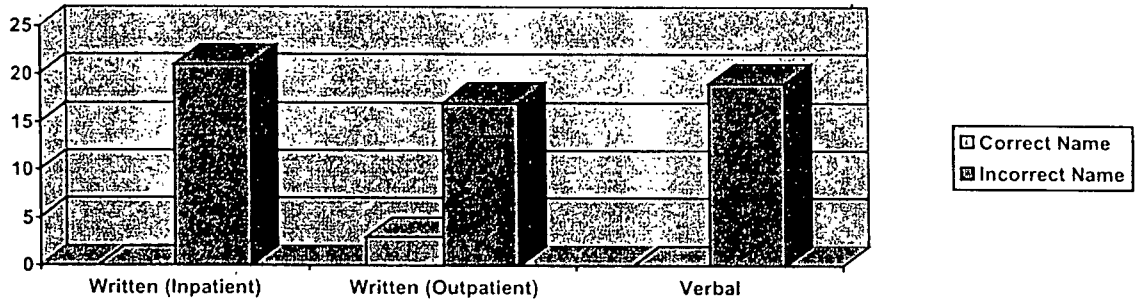
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	[redacted] take one by mouth daily, dispense #30.
Inpatient RX: 	

2. Results:

i. The results for [redacted] are summarized in Table 3.

Table 3

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	31	21 (68%)	0 (0%)	21 (100%)
Written Outpatient	39	20 (51%)	3 (15%)	17 (85%)
Verbal	35	19 (54%)	0 (0%)	19 (100%)
Total	105	60 (57%)	3 (5%)	57 (95%)



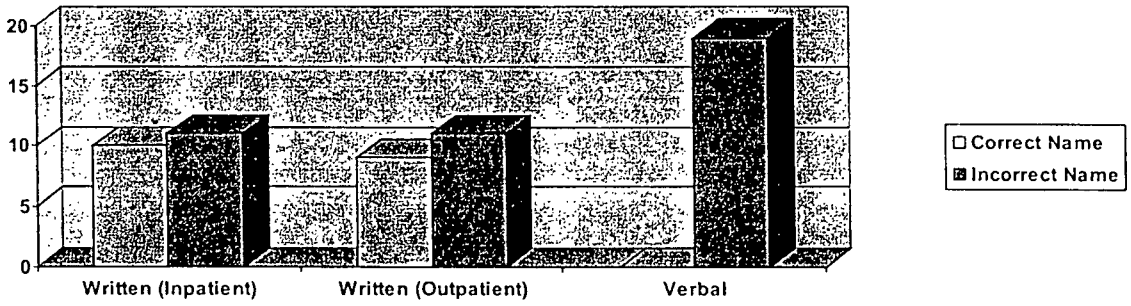
Among the verbal prescription study participants for [redacted] 19 of 19 (100%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted] The incorrect responses were *Eroliess (1), Uralease (3), Uralese (2), Urelease (1),* [redacted] *(1),* [redacted] *(1), Uriles (1), Urileve (1), Urleez (1), Urolease (4), Urolese (1), Urolise (1), and Urolys (1).* None of the interpretations are similar to a marketed drug product.

Among the written prescription study participants for [redacted] 38 of 41 (93%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted] The incorrect responses were *Unaex (1), Unbef (1), Unbex (2), Uncief (2), Unibex (2), Unicef (1), Unicief (1),* [redacted] *(5), Uribex (2), Ureflug (1), Ureley (1),* [redacted] *(1),* [redacted] *(1), Ureluf (7), Urelug (3), Uriluf (3), Uriluj (1),* [redacted] *(1), and Useluf (2).* None of the interpretations are similar to a marketed drug product.

ii. The results are for [redacted] summarized in Table 4.

Table 4

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	31	21 (68%)	10 (48%)	11 (52%)
Written Outpatient	39	20 (51%)	9 (45%)	11 (55%)
Verbal	35	19 (54%)	0 (0%)	19 (100%)
Total	105	60 (57%)	19 (32%)	41 (68%)



Among the verbal prescription study participants for [redacted] 19 of 19 (100%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted] The incorrect responses were *Extreme (17), Ixtreme (1), and* [redacted] *(1).* None of the interpretations are similar to a marketed drug product.

Among the written prescription study participants for [redacted] 22 of 41 (54%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of [redacted] The incorrect responses were *Valtreme (1), Vastreme (1), Vastrene (1), Vatreme (3), Vatrimil (1), Vistreme (1), Vstreme (1), Vstrene (1), Xatreme (1), Xestreme (1), Xgtrence (1), Xsteanre (1), Xstensure (1), Xstremil (1), Xstremme (1), Xstrene (2), Xstrense (1)* [redacted] *(1), and Xytrence (1).* None of the interpretations are similar to a marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT:

1. [redacted]

In reviewing the proprietary name [redacted] the primary concerns raised were related to one proposed proprietary name, [redacted] which is currently under review, and two look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Duricef, and Aricept.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between [redacted] and [redacted] Duricef, or Aricept. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, [redacted] However, a negative finding does not discount the potential for name confusion given the limited predicative value of these studies, primarily due to the sample size.

[redacted]

Duricef and the proposed name [redacted] look similar when scripted (see below). Duricef contains cefadroxil, a cephalosporin antibiotic indicated for the treatment of urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. Depending on the condition being treated, the recommended dose of Duricef can range from 1 to 2 grams per day, given in divided doses. Both names contain seven letters and similar letter combinations at the beginning of each name ("Duri" vs. [redacted] The capital letters "D" and [redacted] can also look similar when scripted. Additionally, the letter combinations at the end of each name ("cef" vs. [redacted] look almost identical when written. Although Duricef has multiple strengths (500 mg, 1 gram, 125 mg/mL, 250 mg/mL, and 500 mg/mL), Duricef and [redacted] do share overlapping numerals in their strengths (1 g vs. 10 mg). Additionally, the products overlap in dosage form (tablets), route of administration (oral), and dosing regimen (once daily). These similarities in addition to the similarities of the look-alike characteristics increase the potential for confusion between Duricef and [redacted] Should a patient receive Duricef instead of [redacted] they would lose the pharmacological effects of [redacted] and would also be at risk for experiencing side effects associated with Duricef. These include gastrointestinal upset, anaphylaxis, rash, and blood dyscrasias.

Duricef [redacted]

Duricef

Aricept and the proposed name [redacted] look similar when scripted (see page 9). Aricept contains the active ingredient donepezil, and is indicated for the treatment of mild to moderate dementia associated with Alzheimer's Disease. The recommended dosage of Aricept is 5 mg or 10 mg daily. Both Aricept and [redacted] contain seven letters and three syllables. Additionally the beginning of each name can look similar when scripted ("Ari" vs. [redacted]). The endings of the names are more distinguishable due to the presence of the letter "p" in Aricept. However, the ending letter combinations of each name share some look-alike characteristics ("cept" vs. [redacted] due to the similarities in the scripted letter combinations "ce" and [redacted] and "t" and [redacted] In addition to the look alike characteristics of the drug products, Aricept and [redacted] also share overlapping strengths (10 mg), dosage form (tablet), route of administration (oral), and dosing regimen (once daily). If an inpatient or outpatient prescription order were written for either drug product for example "Aricept 10 mg qd" or [redacted] 10 mg qd", the similarities in the look-alike characteristics as well as the strength and dosing regimen of the products, would increase the likelihood of drug name confusion. Lastly, Aricept and [redacted] are likely to be used in similar patient populations. Therefore, if a prescription for either medication is written poorly, and misread, the error could remain undetected as either medication would be appropriate for use in

the same patient population. Should a patient receive Aricept instead of [redacted] they would be at risk for experiencing side effects associated with Aricept, such as nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.

Aricept [redacted]

Aricept 10mg [redacted] 10mg

2. [redacted]

In reviewing the proprietary name [redacted] the primary concerns raised were related to two look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Estring and Amnesteem.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between [redacted] and Estring or Amnesteem. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, [redacted] However, a negative finding does not discount the potential for name confusion given the limited predicative value of these studies, primarily due to the sample size.

Estring has the potential to sound similar to the proposed name [redacted] Estring contains estradiol, and is indicated for the treatment of urogenital symptoms associated with postmenopausal atrophy of the vagina and the lower urinary tract. Estring is a vaginal ring that is designed to deliver 7.5 micrograms of estradiol over a 24 hour period, and it is replaced every 90 days. Estring and [redacted] contain two syllables. Additionally, the beginning of each name ([redacted] vs. "Es"), and the ending of the names ([redacted]" vs. "tring") sound identical when pronounced. However, Estring and [redacted] do differ in strength (2 mg vs. 10 mg), dosage form (vaginal ring vs. tablet), route of administration (intravaginal vs. oral), and dosing regimen (every 90 days vs. once daily.) Although there is overlap in the sound-alike characteristics between Estring and [redacted] the differences decrease the chance of confusion between the two products. Lastly, Estring and [redacted] will be used in different patient populations, which will further decrease the likelihood of confusion.

Amnesteem and the proposed name [redacted] can sound similar due to the similarities in the ending of each name ("steem" vs. [redacted]). Amnesteem contains isotretinoin, and is indicated for the treatment of severe recalcitrant nodular acne that has been unresponsive to conventional therapy. Although the endings of the names are phonetically similar, the beginning of each name is clearly different when pronounced ("Amne" vs. [redacted]). Amnesteem and [redacted] do share an overlapping strength (10 mg) and route of administration (oral), however they differ in dosing regimen (twice daily vs. once daily). Additionally, Amnesteem has been designated as a pregnancy category X medication. It is prescribed under the *System to Prevent Isotretinoin-Related Issues of Teratogenicity (S.P.I.R.I.T.)*. This system consists of pregnancy testing in females who are prescribed Amnesteem, as well as counseling in all patients who are prescribed the medication. Patients sign a consent form and meet the pre-determined criteria for treatment with Amnesteem before qualifying stickers are placed on their prescriptions, which can then be filled within 7 days of the date they are written. Also, valid Amnesteem prescriptions can only be dispensed with no more than a 30 day supply of the medication. Refills require a new prescription with the appropriate qualifying stickers. Telephone or computerized prescriptions

for Amnesteem are not permitted. Despite the overlap in strength and route of administration, the lack of convincing sound-alike characteristics in addition to the differences in regimen, as well as the monitoring procedures for Amnesteem, minimizes the likelihood of confusion between the two products.

D. ———————————

1. **Market Research for Proposed Name[ ] dated November 18, 2002**

The ——— conducted a study to evaluate the potential for error between [ ] and currently marketed brand/generic drug products. The[ ] reported that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were: Urologists (50), hospital pharmacists (50), and retail pharmacists (50). Overall, the response rate was 41% for practitioner nomenclature review and 38% for handwritten and verbal analysis. The medical professionals participated in various aspects of the three phases of the[ ] study. The four sections of the study as well as study findings are discussed below.

a. Section A – Practitioner Nomenclature Review: Physicians

[ ] asked 100 physicians to view the test name[ ] and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined if[ ] had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Verbal and handwritten prescriptions of the proposed proprietary name were collected from these physicians to be used in Section B of the study. The physicians provided oral and handwritten interpretations of the following[ ] prescription:

——— *10 mg*
1 tab po qd

DMETS Response:

Although[ ] indicates that 100 physicians were asked to participate in this phase of the study, the response rate was only 38%[ ] notes that this is a "typical" response rate for a survey of this type. However, there are limitations in the predicative value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed. Additionally, DMETS notes that this study asked physicians, instead of pharmacists, to identify any[ ] sound-alike or look-alike products. Physicians do not usually interpret prescriptions and thus the section would have been more effective if pharmacists had been included.

Physicians were requested to identify any hyperbole or false claims implied by ———. Of the physicians polled, 8% of physicians *did* believe that the name was promotional, 6% believed that the name[ ] implies relief from urinary symptoms, 1% thought that it implies relief from urological issues, and 1% believed that it implies relief from BPH symptoms.

Physicians were also requested to identify medical terms or devices that had sound-alike or look-alike properties to [redacted] and to identify any existing names they considered to be similar to [redacted] based on sound, appearance, or both. DMETS concurs with the [redacted] assessment that the six of the seven proprietary names identified by the physicians (*Urimart-T, Urimax, Urised, Urispas, Ursodiol, Uniphyl, Urised, and Ursodiol)* have a low potential for confusion with [redacted] However, DMETS does not concur with [redacted] assessment that Duricef has a low potential for confusion with [redacted] (see page 8 of this review). [redacted] also identified two medical terms that were considered similar to the proposed proprietary name. These were "Urethra and "Urine". These are discussed in section D of the [redacted] study.

b. Section B – Handwritten and Verbal Analysis: Pharmacists

[redacted] provided one hundred pharmacists with a verbal and written prescription for [redacted] The objective of this phase is to determine if any of the sample [redacted] prescriptions would be interpreted as a currently marketed brand or established name product.

DMETS Response:

[redacted] reports that 100% of the pharmacists interpreted the verbal prescription correctly, and 99% of the pharmacists interpreted the handwritten prescription correctly. However, [redacted] states that two hundred sample prescriptions were collected from the physicians (i.e., 100 verbal and 100 written). Therefore, it appears that each of the one hundred pharmacists would have received two sample prescriptions to review, one written and one verbal. This methodology introduces bias because the participating pharmacists would have been exposed to the drug name before evaluation of the second sample.

The single incorrect response cited in the [redacted] study, from a handwritten order, was "Omnicef". Omnicef is a currently marketed cephalosporin antibiotic. The name Omnicef was not identified by DMETS , however upon review, we concur with the [redacted] that the potential for confusion is minimal.

c. Section C – Computer-Assisted Analysis

[redacted] conducted a "comprehensive search of medical references" to identify brand and established name products that may sound-alike or look-alike to the proposed name [redacted] Thirty names were compared to [redacted] using [redacted] database and using a "Phonological and Orthographical Similarity Analysis." The "Phonological and Orthographical Similarity Analysis" identifies a threshold of similarity between [redacted] and the products identified during the search of the medical references. The objective of this analysis is to identify the 'similarity between the proposed proprietary name and any sound-alike or look-alike product'. The proprietary name Relief exceeded the threshold value for the Phonologic Similarity Ratio, a measure of sound-alike similarity, when compared to [redacted] Relief is a decongestant ophthalmic that is available over-the-counter.

DMETS Response:

DMETS agrees with [redacted] that although Relief exceeded the threshold value for Phonologic Similarity Radio, Bigram, Trigram and Edit String Distance, overall, the product has no common features when compared with the profile of [redacted]

d. Section D - Pharmacists' Analysis - Nomenclature Advisory Board (NAB) Review

Five actively practicing retail and hospital pharmacists provided an independent analysis of the proposed proprietary name [redacted] by considering its potential for error and potential for patient harm in the event of an error. The pharmacists were provided with the product concept and profile information for [redacted] as well as research data from all sections of the study, and were asked to evaluate this information. The pharmacists evaluated all of the data obtained during this study. The NAB also considered postmarketing surveillance information, including errors and adverse events as reported in the National Coordinating Council for Medication Error Reporting and Prevention website, MedWatch website, U.S. Pharmacopoeia website, the U.S. Pharmacopoeia Quality Review – Stop, Look, and Listen! list, and the American Drug Index Monograph "Drug Names That Look Alike and Sound Alike". The NAB concluded that although one response was received for Omnicef, Omnicef has no commonalties with [redacted] with the exception for dosage form. The board also stated that the study findings regarding the evaluation of hyperbole or fanciful claims indicated nothing misleading or inappropriate about the proposed proprietary name. Therefore, [redacted] should be considered an appropriate proprietary name.

DMETS Response:

DMETS agrees with the board's contention that Omnicef does not pose a significant risk of confusion with [redacted] However, DDMAC disagrees with the board that the proposed name, [redacted] is not misleading. DDMAC has stated [redacted] implies total relief of benign prostatic hyperplasia symptoms.

2. Market Research for Proposed Name [redacted] dated November 18, 2002

The [redacted] conducted a study to evaluate the potential for error between [redacted] and currently marketed brand/generic drug products, using the BrandTest® BrandReality™ Research Method. BrandTest® BrandReality™ Research is conducted via the Internet using self-administered questionnaires (SAQ). Respondents provided an evaluation of the test drug name [redacted] four different phases of the study. The [redacted] reported that 50 physicians and 50 pharmacists participated in the study. The specialties of the physicians and pharmacists were: Urologists (50), retail pharmacists (50), and hospital pharmacists (50).

a. Phase One (50 Physicians):

[redacted] asked 50 physicians to read the test drug name into the [redacted] voicemail system. The recording allowed for the creation of sound files to be

used in Phase 2 and Phase 4 of the study. Each physician also hand-wrote (in script) the test drug name and faxed this to ———

DMETS Response:

—— indicates that physicians were instructed to write their prescriptions in script. By doing this, — has introduced bias into the study. Generally, when individuals are specifically asked to write something in script, the tendency is to write neatly, and in one's best handwriting. This would not provide a true sample of prescriptions that are seen in both retail and hospital pharmacy settings. Samples of the handwritten prescriptions were not provided to DMETS for review.

b. Phase Two (Pharmacists Panel A – 10 Pharmacists):

—— contacted 10 pharmacists and instructed them to take an on-line survey. The pharmacists listened to names pronounced by physicians in Phase 1, and then typed their interpretations of the physicians' prescriptions. This phase of the study tests for correct spelling in verbatim responses after hearing the name, and whether misspellings are in fact the names or existing brand or generic drugs. Any misspelled names identified were then sent to the ——— ; for a third-party analysis, to determine if any of the names were currently marketed drug products. In addition to the verbal prescription filling portion of the study, pharmacists also performed an "exercise" while taking the on-line survey in which they viewed the handwritten images of each test name (created in Phase 1), and then typed their interpretations of the prescription

DMETS Response:

——reports that 2% (1 of 50) of the pharmacists interpreted the verbal prescription correctly. The incorrectly spelled responses include misspelled variations of the proposed name[redacted] The incorrect responses were: —— *(35), Extrene (5),* —— *(3), Estrine (1),* *(1), Extreve (1), Extrim (1), and Xtream(1).* Although, — states that only 10 pharmacists participated in this phase of the study, and state that the study is "unaided", data is reported for a total of 50 pharmacists. Therefore, it appears that each of the ten pharmacists would have received five verbal prescriptions to interpret. This methodology introduces bias because the participating pharmacists would have multiple exposures to the drug name during the evaluation process. Additionally, —reports that 94% (47 of 50) of the pharmacists spelled the drug name —— correctly after reviewing the handwritten images of each test name previously created in Phase 1. The incorrectly spelled responses include misspelled variations of the proposed name[redacted] The incorrect responses were —— *(2),* and *Xsreme (1).* Additionally, — indicates that pharmacists were asked to participate in this part of the study while taking the on-line verbal prescription survey portion of the study. Thus giving the study participants prior knowledge of the drug name.

c. Phase Three (50 Physicians and 30 Pharmacists):

In this phase of the study, participants were first asked to view the proposed proprietary name and then identify existing proprietary and non-proprietary drug names that sound and/or look alike to the proposed proprietary name. Next, the participants were provided with the product profile, and then shown the test name along with each brand or generic drug that was previously identified as similar. The study participants were asked to select (if any) the aspects of the drug profile that could lead to confusion in prescribing or dispensing the comparison drug, and indicate whether the error with the comparison drug could lead to potential harm. Additionally, in order to test the drug name for hyperbole issues, the participants were asked to identify any misleading connotation, exaggerations, or other hyperboles implied by the test drug name, and explain the nature of the issue.

DMETS Response:

— reports that 96.2% (77 of 80) of the study participants did not identify any other product names that might sound similar to [redacted] The three product names that were identified as having possible sound-alike confusion with [redacted] were: Esidrix, Xanax, and X-Trozine. Additionally, — reports that 97.5% (78 of 80) of the study participants did not identify any other product names that look similar to the proposed product name, [redacted] The 2 product names that were identified as having possible look-alike confusion with [redacted] were: Streptase and Xerac. DMETS agrees with — conclusion that there is a low potential for confusion between these five drug names and the proposed name [redacted] However, we note that none of the study participants indicated the names Estring or Amnesteem as having sound-alike characteristics to [redacted] This may be due to the limited patient populations with which the healthcare providers are familiar, and also with the fact that Amnesteem was recently approved in November, 2002.

Of the study participants who were asked to evaluate the drug name for "hyperbole" issues and to identify any misleading connotations, exaggerations, or other hyperbole implied by the test drug name, — reported that 1.3% believed the name implied the product was an energy supplement, 1.3% believed the name implied that it stops all urine flow, 1.3% that it is a radical new treatment, and 1.3% thought that the product name suggested complete relief. ——— reports that 95% of the physicians and pharmacists polled did not have an issue with the name from a promotional perspective. Stated differently, 5% of the participants *did* believe that the name was misleading.

d. Phase 4 (Pharmacists Panel B – 10 Pharmacists):

In this phase of the study, pharmacists listened to a recording of the test name [redacted] pronounced by the physicians (from Phase 1) and then were instructed to report what they heard in the sound file by selecting one name from a list that included positive and negative control names. Additionally, these pharmacists were also asked to view a handwritten representation of the test name [redacted] which was created in Phase 1, and instructed to report what they viewed by choosing one name from a list that included positive and negative control names.

DMETS Response:

— reports that in the sound-alike accuracy evaluation portion of the study, 96% (48 of 50) of the pharmacists chose the correct drug after hearing the name. Also, 100% (50 of 50) of the pharmacists chose the correct drug name from a list after seeing the handwritten prescriptions. Although — states that only 10 pharmacists participated in this phase of the study, data is reported for a total of 50 pharmacists. Therefore, not only would each pharmacist have multiple exposures to the drug name, but the pharmacists were provided a list of possible drug names to choose from. This not only introduces bias into the study, but also does not represent a real world environment in regards to either retail or hospital pharmacy work settings.

e. Orthographic String Similarity Testing (OSST):

OSST is a technique used to identify the degree of similarity between two words based on their letter construction. —performed an analysis using the OSST method for the five drug names (Esidrix, Xanax, X-Trozine, Streptase, and Xerac) that were found to have sound and/or look-alike characteristics to the proposed name in Phases 3 and 4 of the study. — also included a pharmacists analysis of the drug names from the In each case, it was determined that the drug reviewed did not have a high potential for confusion with

DMETS Response:

DMETS agrees with the conclusion that there is little potential for confusion between the proposed name and the drug products Esidrix, Xanax, X-Trozine, Streptase, and Xerac.

III. LABELING, PACKAGE AND SAFETY ERLATED ISSUES

Container labels, carton and insert labeling were previously reviewed under the proprietary name — (Consult # 00-0191).

IV. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name However, DMETS has no objections to the use of the proprietary name from a safety perspective.

In reviewing the proprietary name the primary concerns raised were related to two look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Duricef, and Aricept.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between and Duricef, or Aricept. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name However, a negative finding does not discount the potential for name confusion given the limited predicative value of these studies, primarily due to the sample size.

Duricef and the proposed name [redacted] look similar when scripted (see below). Duricef contains cefadroxil, a cephalosporin antibiotic indicated for the treatment of urinary tract infections, skin and skin structure infections, pharyngitis, and tonsillitis. Depending on the condition being treated, the recommended dose of Duricef can range from 1 to 2 grams per day, given in divided doses. Both names contain seven letters and similar letter combinations at the beginning of each name ("Duri" vs. " — "). The capital letters "D" and —" can also look similar when scripted. Additionally, the letter combinations at the end of each name ("cef" vs. "—") look almost identical when written. Although Duricef has multiple strengths (500 mg, 1 gram,
125 mg/mL, 250 mg/mL, and 500 mg/mL), Duricef and [redacted] do share overlapping numerals in their strengths (1 g vs. 10 mg). Additionally, the products overlap in dosage form (tablets), route of administration (oral), and dosing regimen (once daily). These similarities in addition to the similarities of the look-alike characteristics increase the potential for confusion between Duricef and [redacted] Should a patient receive Duricef instead of [redacted] they would lose the pharmacological effects of [redacted] and would also be at risk for experiencing side effects associated with Duricef. These include gastrointestinal upset, anaphylaxis, rash, and blood dyscrasias.

Duricef [redacted]

Aricept and the proposed name, [redacted] look similar when scripted (see below). Aricept contains the active ingredient donepezil, and is indicated for the treatment of mild to moderate dementia associated with Alzheimer's Disease. The recommended dosage of Aricept is 5 mg or 10 mg daily. Both Aricept and [redacted] contain seven letters and three syllables. Additionally the beginning of each name can look similar when scripted ("Ari" vs. " — "). The endings of the names are more distinguishable due to the presence of the letter "p" in Aricept. However, the ending letter combinations of each name share some look-alike characteristics ("cept" vs. " — ") due to the similarities in the scripted letter combinations "ce" and "—", and "t" and —. In addition to the look alike characteristics of the drug products, Aricept and [redacted] also share overlapping strengths (10 mg), dosage form (tablet), route of administration (oral), and dosing regimen (once daily). If an inpatient or outpatient prescription order were written for either drug product for example "Aricept 10 mg qd" or [redacted] 10 mg qd", the similarities in the look-alike characteristics as well as the strength and dosing regimen of the products, would increase the likelihood of drug name confusion. Lastly, Aricept and [redacted] are likely to be used in similar patient populations. Therefore, if a prescription for either medication is written poorly, and misread, the error could remain undetected as either medication would be appropriate for use in the same patient population. Should a patient receive Aricept instead of [redacted] they would be at risk for experiencing side effects associated with Aricept, such as nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.

Aricept [redacted]

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name [redacted] However, DMETS has no objections to the use of the proprietary name [redacted] from a safety perspective. DMETS decision is tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

B. DMETS requests submission of the container label, carton and insert labeling when available.

C. DDMAC does not recommend the use of the names [redacted] and [redacted] from a promotional perspective for the following reasons: The name [redacted] is misleading and implies total relief of benign prostatic hyperplasia (BPH) symptoms, and the name [redacted] is not acceptable because it is overly fanciful.

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 Sammie Beam, Project Manager, at (301)827-3242.

/S/

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tia Harper-Velazquez
5/12/03 07:45:05 AM
PHARMACIST

Carol Holquist
5/12/03 09:38:32 AM
PHARMACIST

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 04/25/01	DUE DATE: 05/25/01	OPDRA CONSULT #: 00-0093

TO:

Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Evelyn R. Farinas
Project Manager
HFD-580

PRODUCT NAME: Uroxatral (alfuzosin tablets) 10 mg **NDA:** 21-287	**MANUFACTURER:** Sanofi-Synthelabo Group **DISTRIBUTOR:** Sanofi-Synthelabo, Inc

SAFETY EVALUATOR: David Diwa, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA has performed a review of the proposed proprietary name Uroxatral to determine the potential for confusion with approved proprietary and generic drug names as well as names pending drug marketing approval.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Uroxatral.

☒ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 18, 2001

NDA: 21-287

NAME OF DRUG: **Uroxatral** (alfuzosin HCl tablets) 10 mg

NDA HOLDER: Sanofi-Synthelabo Group

I. INTRODUCTION

This consult is written in response to a request from the Division of Reproductive and Urologic Products for assessment of the proposed proprietary drug name, Uroxatral, regarding potential name confusion with other proprietary and generic drug names. The sponsor previously submitted the proprietary name _____ which OPDRA did not recommend for approval due to safety concerns (OPDRA Consult 00-0191).

PRODUCT INFORMATION

The proposed product, Uroxatral, contains alfuzosin hydrochloride, a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors. Uroxatral relaxes smooth muscle tone through its activity at alpha$_1$-adrenoreceptors which are abundantly located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. The product is indicated for the treatment of signs and symptoms of benign prostatic hyperplasia, and not indicated for the treatment of hypertension. The recommended dose is 10 mg daily to be taken right after the same meal each day. Uroxatral will be supplied as 10 mg tablets in bottles of 30 and 100 tablets. It will also be available in blister packs for hospital use.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3,4] as well as several FDA databases[5] for existing drug names which sound alike or look alike to Uroxatral to a degree where potential confusion between drug names could occur under usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K, (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Information Handbook 1999-2000, Lacy CF, Armstrong LL, Goldman MP, Lance LL (eds) Lexi-Comp Inc, Hudson

[5] The Established Evaluation System [EES], the Labeling and Nomenclature [LNC] database of proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database was also conducted[6]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies and one verbal prescription study, involving health care practitioners within the FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the proposed name Uroxatral.

A. EXPERT PANEL DISCUSSION

1 OPDRA held an Expert Panel discussion to gather professional opinions on the safety of the proprietary name, Uroxatral. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The panel is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel identified several product names, which they believed pose potential risk for name confusion with Uroxatral. They were most concerned with Ursodiol. The identified products are listed in the table below with a summary of available dosage forms and usual FDA-approved dosages.

2 DDMAC

DDMAC did not have any promotional concerns regarding the proposed name.

Product Name	Dosage form(s); Generic name	Usual Dose	Observation
Uroxatral	Alfuzosin; 10 mg tables	10 mg PO QD with a meal	
Ursodiol	Ursodiol; 300 mg capsules	8-10 mg/kg/day in 2-3 divided doses	*LA/SA
Urogesic	Phenazopyrindine; 100 mg tablets	100-200 mg TID	*LA/SA
Rocaltrol	Calcitriol; 0.25, 0.05 mcg capsules 1 mcg/mL, 2 mcg/mL injectable 1 mcg/mL oral solution	0.25 mcg PO QD or every other day 0.5 mcg/day 3 times weekly IV	*LA

*SA = Sound-alike
*LA = Look-alike

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

OPDRA conducted three studies involving 85 health professionals comprised of pharmacists, physicians, and nurses within the FDA. The objective was to test the degree of name confusion between Uroxatral and other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Uroxatral (see page 4). These prescriptions were scanned into a computer and subsequently delivered to a random sample of the participating health professionals via e-mail. In addition, a verbal order was recorded on voice mail. The voice mail message was then sent to a random sample of the participating health

[6] WWW location http:// www.uspto.gov/tmdb/index.html.

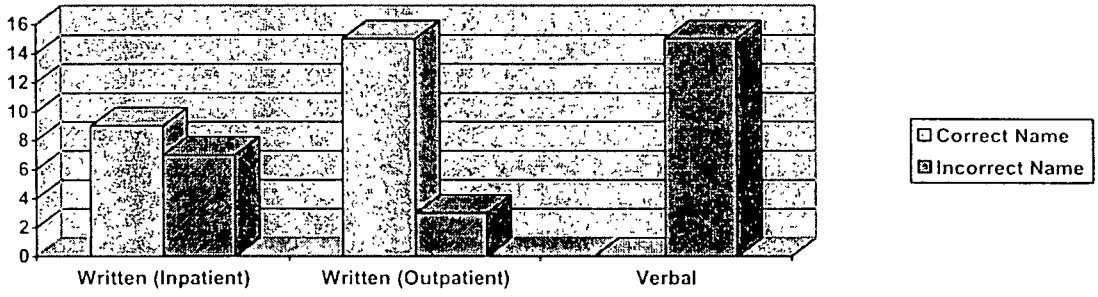
professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX : Uroxatral Sig: 1 PO QD #30	Verbal RX : Uroxatral 1 PO QD # 30
Inpatient RX Order: Uroxatral 10 mg PO QD	

2. The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	27	16 (59%)	9 (56%)	7 (44%)
Written Outpatient	30	18 (60%)	15 (83%)	3 (17%)
Verbal	28	14 (50%)	0 (0%)	14 (100%)
Total	85	48 (56%)	24 (50%)	24 (50%)



Fifty percent of all study participants responded incorrectly to the name Uroxatral. Written and verbal scores of the incorrect responses are summarized in Table II on page 5.

All responses were misspelled or phonetic variations of the proposed drug name. Almost all misspellings involved a modification of the last six letters especially in the verbal study where all responses were incorrect. There were fewer misspellings in the written outpatient prescription study (17%) compared to the written inpatient study (44%), which we believe was due to the penmanship. The inaccurate interpretation of the proposed drug name did not overlap with any currently marketed drug product.

Table II

Incorrectly Interpreted	
Written Inpatient	Uroxattal (4)
	Uroxcitrol
	Uroxitral
	Uroxittal
Written Outpatient	Moxatral
	Moxatrol
	Uroxotral
Verbal	Eurogetrol
	Urasachel
	Urazechel
	Urosajil
	Urovachal
	Urovitro
	Urozaetrral
	Urozatril (4)
	Urozatrol (2)
	Urozatryl

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Uroxatral, the expert panel identified Ursodiol, Urogesic and Rocaltrol as products with the most potential for sound-alike/look-alike name confusion.

Ursodiol is a gallstone dissolution agent orally administered at an average dose of 8-10 mg/kg/day in 2-3 divided doses. Urosodiol is available in 300 mg oral capsules compared to Uroxatral which will be provided in 10 mg oral tablets. Although Ursodiol looks and sounds like Uroxatral, the two product have different indications, pharmacologic activity, dosage strength and dosing interval. The risk of a product mix-up between Ursodiol and Uroxatral appears to be low.

Urogesic (phenazopyridine) is a urinary tract analgesic with local anesthetic activity. It is used in the symptomatic relief of urinary burning, itching, frequency and urgency in association with urinary tract infection or following urologic procedures. Urogesic is usually administered at a dose of 100 to 200 mg three times a day after meals for 2 days, and then used concomitantly with antibiotic therapy. The product is available in oral tablet formulations of 95 mg, 100 mg and 200 mg. An extemporaneous preparation of 10 mg/mL oral suspension can be made from oral tablets. Unlike Urogesic, Uroxatral will only be available in 10 mg oral tablet formulations. Although a patient on Uroxatral may be prescribed Urogesic during a urologic procedure, differences in indication, pharmacologic activity, dosage strength and dosing interval make it unlikely that these two products will be mixed-up. Moreover, Uroxatral will be taken on a maintenance basis while Urogesic is used for symptomatic relief.

Rocaltrol (calcitriol) is a vitamin D product. It is a fat soluble vitamin used in the management of hypocalcemia, especially in the treatment of patients on renal dialysis. The product is also used to reduce elevated parathyroid hormone levels. Calcitriol is available as an injectable, oral solution and capsule dosage form. The oral dose is 0.25 mcg/day every other day or 0.5 mcg/day

3 times a week. Rocaltrol looks like Uroxatral when scripted. The block of characters for the two product names are similar in that both have 9 letters and Rocatrol ends with "altrol" and the Uroxatral with "atral". In addtiton, the first three letters of both drug names contain "ro". However, Rocaltrol is dosed in "mcg" whereas Uroxatral is dosed in "mg". In addition, differences in indication, dosage strength and dosing interval make the potential risk of a product mix-up between Rocaltrol and Uroxatral minimal.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

Container labels, carton and insert labeling were previously reviewed under [redacted] (see OPDRA Consult 00-0191).

IV. RECOMMENDATIONS

OPDRA has no objection to the use of the proprietary name Uroxatral.

OPDRA 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 any questions or need clarifications, please contact David Diwa at 301-827-0892.

/S/

David Diwa, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Diwa
5/25/01 09:59:11 AM
PHARMACIST

Jerry Phillips
5/25/01 10:01:38 AM
DIRECTOR

Martin Himmel
5/30/01 12:57:15 PM
MEDICAL OFFICER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 01/24/01	DUE DATE: 08/24/01	OPDRA CONSULT #: 00-0191

TO: Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Products
HFD-580

THROUGH: Evelyn R. Farinas
Project Manager
HFD-580

PRODUCT NAME:	MANUFACTURER: Sanofi-Synthelabo Group
[redacted] (Alfuzosin tablets) 10 mg NDA #: 21-287	DISTRIBUTOR: Sanofi-Synthelabo, Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name, [redacted] to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, [redacted]

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the Name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 23, 2001

NDA NUMBER: 21-287

NAME OF DRUG: Xatral (alfuzosin tablets)
10 mg

NDA HOLDER: Sanofi-Synthelabo Group

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Products for assessment of the proposed proprietary drug name Xatral, regarding potential name confusion with other proprietary/generic drug names. Xatral® is an approved proprietary name for the same active ingredient, alfuzosin, in Europe. The sponsor, Sanofi-Synthelabo, would "like to maintain brand name consistency in the United States."

PRODUCT INFORMATION
The proposed product, Xatral, contains alfuzosin hydrochloride. Alfuzosin is a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors, which are abundantly located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. Alfuzosin relaxes the smooth muscle tone. Alfuzosin is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia, and it is not indicated for the treatment of hypertension. The recommended dose is 10 mg daily to be taken right after the same meal each day. The tablet should not be chewed or crushed. Xatral will be supplied as 10 mg tablets in bottles of 30 and 100 tablets. It will also be supplied in blister packs for hospital use.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to *Xatral* to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).
[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.
[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.
[v] WWW location http:// www.uspto.gov/tmdb/index.html.

conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, *Xatral*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Several products were identified in the Expert Panel Discussion that was thought to have potential for confusion with *Xatral*. These products are listed in the table (page 4), along with the dosage forms available and usual FDA-approved dosage.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other
Xatral	Alfuzosin 10 mg tablets	10 mg po QD with meals	
Sectral	Acebutolol 200 mg, 400 mg capsules	Hypertension: 400 mg QD or 200 mg BID. Maximum dose=200 mg in divided doses. Ventricular arrhythmias: 200 mg BID, then increase to provide an adequate clinical response. Usal daily dosage= 600 to 1,200 mg	S/A per OPDRA
Zestril	Lisinopril 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg tablets	Hypertension: Initial dose: 10 mg QD. Maintenance dose: 20 to 40 mg QD Maximum dose: 80 mg daily. Heart failure: Initial dose: 5 mg QD up to 20 mg QD. Acute myocardial infarction: Initially, 5 mg; then give 5 mg in 24 hours, 10 mg in 48 hours, and 10 mg daily for 6 weeks. In patients with acute MI with low systolic blood pressure (below 120 mm Hg), give 2.5 mg when treatment is started or during the first 3 days after an infarct. If hypotension occurs, a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed.	S/A per OPDRA
Detrol, Detrol LA	Tolterodine 1 mg, 2 mg tablets, 2 mg, 4 mg extended-release tablets	Detrol: 1 mg to 2 mg BID Detrol LA: 2 mg to 4 mg QD	S/A per OPDRA
Zantryl	Phentermine hydrochloride	No longer marketed.	S/A per OPDRA
Statrol	Neomycin sulfate/Polymyxin B Sufate opthalmic solution and ointment	No longer marketed.	S/A per OPDRA
Xanax	Alprazolam 0.25 mg, 0.5 mg, 1 mg, 2 mg tablets 0.1 mg/mL, 1 mg/mL oral solution	Anxiety and tension: Initial: 0.25 mg to 0.5 mg TID. Increase dose prn q 3 to 4 days. Maximum dose=4 mg in divided doses. Painic disorder: Initial: 0.5 mg TID. Increase prn q 3 to 4 days in increments of 1 mg daily. Dosages from 1 to 10 mg daily have been used.	L/A per OPDRA
Xalatan	Latanoprost 0.005% (50 µg/mL) opthalmic solution 2.5 mL	One drop (1.5µg) in the affected eye(s) once daily in the evening.	L/A per OPDRA
		*Frequently used, not all-inclusive	**L/A (look-alike), S/A (sound-alike)

A number of sound-alike product names were identified in the OPDRA Expert Panel as described above. Of these products, Sectral, Zestril, Xanax, Detrol, and Xalatan were considered to be most significant, because they sound and/or look like the proposed name, Xatral. Although Zantryl and Statrol sound similar to the proposed name, Xatral, they are no longer marketed in the United States.

2. DDMAC did not have any concerns about the names with regard to promotional claims.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

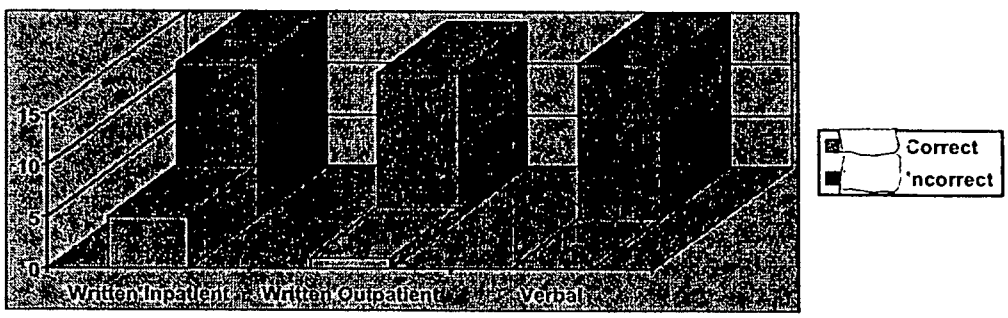
Three separate studies were conducted within FDA, to determine the degree of confusion of Xatral with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 87 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Xatral. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS: Xatral	VERBAL PRESCRIPTIONS
Outpatient: Xatral 10 mg 1 po QD #30 No refills	*Outpatient:* Xatral one daily. #30 No refills
Inpatient: (Xatral)10 mg po qd.	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	Xatral response	Other response
Written: Inpatient	29	20 (69 %)	5 (25 %)	15 (75 %)
Outpatient	30	15 (50 %)	1 (7 %)	14 (93 %)
Verbal: Outpatient	28	15 (53 %)	0 (0 %)	15 (100 %)
Total:	87	50 (57 %)	6 (12 %)	44 (88 %)



Among the written prescription study participants for Xatral, 29 of 35 (83 %) participants interpreted the name incorrectly. Eighteen respondents interpreted the name as *Xatrol,* which differs from the proposed name, Xatral, by one letter. Other incorrect responses were *Tatral, Katrol, Natrol, Xatrel, Xartol, Yatrol, and Yatril.* None of the misinterpretations overlapped with currently approved drug names.

Among the verbal prescription study participants for Xatral, all 15 of 15 (100 %) participants interpreted the name incorrectly. *Four participant interpreted the name incorrectly as "Zestril" (Lisinopril), a currently marketed drug product. One participant interpreted the name incorrectly as "Detrol" (Tolterodine), a currently marketed drug product.* Other incorrect responses were *Zadrel, Vatrol, Zatril, Naturale, Zestril, Zachel, Zattril, and Zatural.*

C. STUDY SUBMITTED BY APPLICANT

Sanofi-Synthelabo, NDA holder of Xatral, had requested the ——— to evaluate the proposed proprietary name, Xatral. ——— study included seventy-five urologists in office-based practice and forty-five pharmacists. They were asked to identify existing brand/generic drug names that sound and look like the proposed proprietary name, Xatral. The sponsor did not provide sufficient information on its methodology to allow for assessment of appropriateness. Hence, the study was not forwarded to OPDRA epidemiologists for review and comment.

According to the results submitted by the ——— 113 of 120 (94%) respondents did not identify any existing brand/generic drug names that sound alike to the proposed name, Xatral. 107 of 120 respondents (89%) did not identify any existing brand/generic drug names that look alike to the proposed name, Xatral. The respondents identified nine sound alike/look-alike names. The names that were discovered by one to five percents of the respondents are listed in the following table, along with the dosage forms:

Brand Name	Dosage Form
Xenical	120 mg Capsule
Zestril	2.5, 5, 10, 20, 30, 40 mg tablet
Citrical	200 mg tablet, 315 mg caplet, 500 mg effervescent tablet
Xanax	0.25, 0.5, 1.0, 2.0 mg tablet
	Not Approved
Xalatan	2.5 mL opthalmic solution
Ex-Lax	OTC
Xerac	OTC topical agent
Zantac	25 mg/mL injection, 150 mg tablet, capsule, effervescent tablet; 300 mg tablet and capsule; 150 mg effervescent granules and syrup

In conclusion, Sanofi-Synthelabo stated that there is a low risk for confusion between the proposed proprietary name, Xatral and the above product names for several reasons. First, Xatral has distinctive appearance. Second, there is no overlap between the proposed product, Xatral, and the products identified by the ———. Finally, the dosage regimen for "Xatral is quite specific (10 mg once daily without dose-titration). However, the sponsor admitted that Zestril is also available in 10 mg dosage units, similar to the proposed product, Xatral.

D. SAFETY EVALUATOR RISK ASSESSMENT

We conducted prescription studies to simulate the prescription ordering process. *In this case, there was a suggestion that Xatral could be confused with Zestril and Detrol as discussed in the Expert Panel Discussion.* Four respondents from the verbal study provided *Zestril* as an interpretation. One respondent from the verbal study provided *Detrol* as an interpretation. Although there are limitations to the predictive value of these studies, primarily due to the small sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Four participants from the verbal study interpreted the name as *Zestril.* Zestril, lisiniopril, is indicated for the treatment of hypertension and for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Zestril is also indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis. Not only the names Xatral and Zestril, sound alike, they share overlapping strengths, dosing schedules and dosage forms. Xatral is available as 10 mg tablets and it is dosed once daily. Zestril is also supplied in 10 mg tablets and it is dosed once daily too. If a verbal prescription for "Zestril 10 mg po QD" is misinterpreted as "Xatral 10 mg po QD," serious patient harm could. The omission of Zestril could be detrimental in patients with acute myocardial infarction. The ACE inhibitors have been shown to improve survival rate in patients with acute myocardial infarction if ACE inhibitors are used in hemodynamically stable patients within 24 hours of acute myocardial infarction.

The prescription study also confirmed confusion between Xatral and *Detrol.* **One** respondent from the verbal study interpreted the name as Detrol. Detrol, tolterodine, is indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. Not only Xatral and Detrol sound alike, they share overlapping dosage forms and doing schedules. Detrol is available as 1 mg and 2 mg tablets and the recommended dose is 1 to 2 mg twice daily. However, it is also available in long-acting formulation, Detrol LR. Detrol LR is available as 2 mg and 4 mg tablets and the recommended dose is 2 to 4 mg once daily. Furthermore, both drugs are often used in the same patient population, geriatric patients, further increasing the risk of medication errors.

Xatral and *Sectral* are phonetically very similar according to the expert panel. However, the prescription study conducted by OPDRA did not confirm confusion between Xatral and *Sectral.* Sectral (acebutolol HCl) is a selective, hydrophilic beta-adrenoreceptor blocking agent with mild intrinsic sympathomimetic activity for use in treating patients with hypertension and ventricular arrhythmia. Sectral capsules are provided in two dosage strengths, which contain 200 or 400 mg of acebutolol, and it is dosed twice daily. Xatral and Sectral do not share overlapping strengths and dosing schedules, however, potential for name confusion is possible, because these names are phonetically very similar. Therefore, the proprietary name, Xatral, is objectionable in accordance with 21 CFR 201.10 (c) (5).

The proposed name, Xatral, and *Xanax*, look similar when scripted, and could be confused as demonstrated in the following written sample of prescription:

In the review of the container label, carton labeling, and the package insert for Xatral, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error. (SEE IV)

IV. LABELING, PACKAGING AND SAFETY RELATED ISSUES

A. CONTAINER LABEL/CARTON LABELING

1. On the draft container, we recommend decreasing the prominence of quantity, *30 tablets and 100 tablets,* by decreasing its font size so that it appears smaller than the strength, *10 mg.* We also recommend relocating the net quantity to the bottom of the container label in order not to detract attention away from the strength.

2. Please note that the route of administration for oral use is not required to appear on the container label in accordance with 21 CFR 201.100 (b) (3) and may be deleted.

3. We recommend deleting the logo that is incorporated in the proprietary name. Because of the logo, "Xatral" looks like "Yatral." The logo also obstructs the established name.

4. We recommend adding the statement, "*USUAL DOSAGE: One tablet daily*" in accordance with 21 CFR 201.55.

5. On the draft container label, the current expression of the established name is misleading and incorrect since Xatral is available as extended-release tablets. Also, the strength of alfuzosin hydrochloride is missing on the label. We recommend revising the format of proprietary and established names as follows:

[redacted]
(Alfuzosin HCL Extended-Release Tablets)
10 mg

B. HOSPITAL UNIT DOSE BLISTER PACK

See 2 and 5 under A.

C. PACKAGE INSERT

1. Description

We recommend revising the statement, "Each [redacted] (alfuzosin hydrochloride) tablet contains 10 mg..." to read "Each [redacted] (alfuzosin hydrochloride) extended-release tablet contains 10 mg..."

2. How Supplied/Dosage and Administration

In these sections, we recommend adding the strength of alfuzosin hydrochloride, *10 mg.*

V. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary names "Xatral".

B. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim at 301-827-3242.

/S/

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

/s/

Hye-Joo Kim
3/6/01 01:19:01 PM
PHARMACIST

Jerry Phillips
3/6/01 03:37:25 PM
DIRECTOR

Martin Himmel
3/8/01 12:30:45 PM
MEDICAL OFFICER

..ing, Jean

From: Best, Jeanine A
Sent: Thursday, June 12, 2003 3:44 PM
To: King, Jean; Benson, George; Griebel, Donna J; Beitz, Julie G; Whitaker, Marcea; Jarugula, Venkateswa R; Parekh, Ameeta; Rhee, Moo Jhong; McLeod, Laurie L; Kulick, Corrine
Subject: RE: NDA21-287 patient package insert

uroxatralppi06 1203.doc

I will not be able to make a meeting this afternoon, but attached below are a few suggested edits for the PPI (edits done in track-changes). Also, consider adding back the following information on QTc prolongation under side effects if you wish patients to have this information:

DRAFT LABELING

Thanks,
Jeanine

-----Original Message-----
From: King, Jean
Sent: Thursday, June 12, 2003 3:22 PM
To: Benson, George; Griebel, Donna J; Beitz, Julie G; Whitaker, Marcea; Jarugula, Venkateswa R; Parekh, Ameeta; Rhee, Moo Jhong; McLeod, Laurie L; Kulick, Corrine; Best, Jeanine A
Subject: FW: NDA21-287 patient package insert

here is their proposed PPI.

Jeanine and Corrine--we will be going back on a tcon shortly with the sponsor to discuss our changes to the PI that will be faxed to them with rephrased Phase IV commitment statement. I am not sure of room location yet, but if you can make it, I will let you know where and when. Otherwise, we would appreciate your taking some time now to review their PPI as compared to your comments and provide us feedback if indicated if you can not attend tcon. thank you. Jean

-----Original Message-----
From: Jon.Villaume@us.sanofi.com [mailto:Jon.Villaume@us.sanofi.com]
Sent: Thursday, June 12, 2003 3:08 PM
To: kingje@cder.fda.gov
Subject: NDA21-287 patient package insert

Jean,

r comments on your draft of the PPI are highlighted.

Jon

(See attached file: ALFUZOSIN DRAFT PATIENT INFORMATION DRAFT 12 June 2003.doc)

APPEARS THIS WAY
ON ORIGINAL

4 pages redacted from this section of the approval package consisted of draft labeling

Office of Drug Safety

Memo

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

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Jean King
Project Manager
HFD-580

Date: June 9, 2003

Re: ODS Consult 01-0093-2; Uroxatral (Alfuzosin Hydrochloride Tablets) 10 mg; NDA 21-287.

This memorandum is in response to a June 2, 2003 request from your Division for a re-review of the proprietary name, Uroxatral. Labels and labeling were not submitted for review.

Since the completion of our initial review of the proprietary name Uroxatral, conducted on May 18, 2001 (ODS consult 01-0093), DMETS has identified one additional proprietary name, Carbatrol, which has the potential for confusion with Uroxatral.

Carbatrol and Uroxatral have the potential to look similar. Carbatrol is the proprietary name for carbamazepine and is indicated for the treatment of epilepsy and pain associated with trigeminal neuralgia. Carbatrol is available as extended-release capsules. The recommended initial dose for

adults is 200 mg twice daily with maintenance doses ranging from 800 mg to 1200 mg per day in 3 to 4 divided doses. The recommended initial dose for children is 100 mg twice daily with maintenance doses ranging from 400 mg to 800 mg given in 3 to 4 divided doses. When scripted the letter "C" in Carbatrol can look similar to the "U" in Uroxatral and the ending "atrol" vs. "atral" are almost identical. However, the "arb" in Carbatrol vs. the "rox" help distinguish one name from the other. Although Carbatrol and Uroxatral do not share an overlapping strength (10 mg vs. 100 mg, 200 mg, and 300 mg), they share a numerically similar strength (10 mg vs. 100 mg). However, the products differ in dosing regimen (once daily vs. 2-4 times daily), dose, and indication (benign prostatic hyperplasia vs. epilepsy and pain associated with trigeminal neuralgia). Additionally, the products will not be stored next to each other on pharmacy shelves. Therefore, given the differences and a lack of convincing look-alike potential, confusion between Carbatrol and Uroxatral is minimal.

CARBATROL UROXATRAL

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alina Mahmud
6/10/03 10:27:25 AM
PHARMACIST

Carol Holquist
6/10/03 11:51:06 AM
PHARMACIST

MEMORANDUM

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

DATE: June 3, 2003

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

VIA: Jean King, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for [redacted] alfuzosin HCL extended-release tablets), NDA 21-287

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for [redacted] (alfuzosin HCL extended-release tablets), NDA 21-287. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

4 pages redacted from this section of the approval package consisted of draft labeling

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
6/3/03 12:37:06 PM
CSO

Toni Piazza Hepp
6/3/03 04:53:53 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

PID#: D010494

DATE: January 29, 2002

FROM: Denise P. Toyer, Pharm.D.
Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

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

SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW
Consult:
Drug: Tamsulosin, Terazosin, Doxazosin, Alfuzosin
Reaction: QT Prolongation, Torsades de Pointes, Ventricular Arrhythmias

EXECUTIVE SUMMARY

The Division of Reproductive and Urologic Drug Products forwarded a consult to the Division of Drug Risk Evaluation requesting information on postmarketing adverse event data—QT prolongation, Torsade de Pointes, and ventricular arrhythmia—for tamsulosin, terazosin, and doxazosin and any foreign postmarketing adverse event data for alfuzosin. All of the drugs are used to treat benign prostatic hypertrophy. Alfuzosin received an approvable action on October 5, 2001. Data in the alfuzosin new drug application submission identified QT prolongation as a potential adverse event.

AERS was searched using the MedDRA High Level Term "Ventricular Arrhythmias and Cardiac Arrest" and the Preferred Terms "Electrocardiogram QRS Complex Prolonged," "Electrocardiogram QT Corrected Interval Prolonged," "Electrocardiogram QT Prolonged," and "Torsade de Pointes." The search identified sixteen, fifty-four, and seventy-eight-unduplicated cases for tamsulosin, terazosin, and doxazosin, respectively. Nine cases of arrhythmias and two cases each of Torsade de Pointes and QT prolongation were identified. One case of Torsade de Pointes was reported with tamsulosin and one with terazosin. The tamsulosin case contained limited data and the terazosin case was confounded by the co-administration of Cisapride. The two QT prolongation cases were reported with terazosin and doxazosin. One case involved the concomitant use of Cisapride, whereas in the other, terazosin was discontinued 4 days prior to the adverse event.

OPDRA requested a search of the World Health Organization's (WHO) adverse event database for any data on cardiovascular events reported with alfuzosin. The most prevailing cardiovascular terms from the WHO's database (line listing only) were hypotension (57), syncope (53), postural hypotension (42), palpitations (28), angina (14), myocardial infarction (14), tachycardia (13), and atrial fibrillation (13).

The specific terms QT prolongation and Torsade de Pointes are not included in the WHO line listing. Reports of arrhythmias were identified in the alfuzosin WHO postmarketing data, however, the WHO line listings do not provide sufficient data to determine if a signal exists between the postmarketing alfuzosin data and QT prolongation, Torsade de Pointes, and ventricular arrhythmias.

Specific cases of QT prolongation, Torsade de Pointes, and ventricular arrhythmias were identified in the overview of the postmarketing data for tamsulosin, terazosin, and doxazosin. However, these cases were not compelling and contained confounding factors which make causality assessment difficult.

INTRODUCTION

The Division of Reproductive and Urologic Drug Products forwarded a consult to the Division of Drug Risk Evaluation requesting information on postmarketing adverse event data—QT prolongation, Torsade de Pointes, and ventricular arrhythmia—for tamsulosin, terazosin, and doxazosin and any foreign postmarketing adverse event data for alfuzosin. Alfuzosin, indicated for the treatment of benign prostatic hypertrophy (BPH), has not been approved in the United States and the NDA received an approvable action on October 5, 2001. Data in the new drug application submission identified QT prolongation as a potential adverse event reported with alfuzosin. DRUDP wanted to know if any alfuzosin spontaneous foreign post-marketing data existed.

Tamsulosin, terazosin, and doxazosin are alpha-1-selective adrenoceptor blocking agents that are also used in the treatment of BPH. In order to evaluate the potential risk:benefit ratio between alfuzosin and other agents used to treat BPH, DRUDP wanted a review of the cardiovascular postmarketing data available for tamsulosin, terazosin, and doxazosin. This review should specifically address the terms QT prolongation, Torsade de Pointes, and ventricular arrhythmia.

Labeling

Only two cardiovascular events are listed in the labeling for Flomax (tamsulosin hydrochloride) Capsules. A detailed description of the signs and symptoms of orthostasis is presented in the Adverse Reactions section. The Post-Marketing Experience subsection notes infrequent reports of palpitations.

The labeling for Hytrin (terazosin) notes postural hypotension, palpitations, syncope, and hypotension as potential adverse events found in the benign prostate hypertrophy (BPH)

clinical trials. The hypertension trials identified tachycardia, arrhythmia, and vasodilation.

Hypotension was the most common cardiovascular adverse event identified in clinical trials using Cardura (doxazosin) for BPH. Palpitation, angina pectoris, syncope, and tachycardia were also identified in the BPH clinical trials. Additional cardiovascular adverse events identified in the hypertension clinical trials include dizziness, vertigo, edema, arrhythmia, peripheral ischemia, myocardial infarction, and cerebrovascular accident. The Post-Marketing Experience subsection lists bradycardia as a potential cardiovascular adverse event.

Literature Review

As of January 8, 2002, a EMBASE LIVE search of the published English-language literature, using the following terms: doxazosin, terazosin, tamsulosin, Torsade de Pointe, ventricular arrhythmias, and QT prolongation did not identify references pertaining to the drugs causing the aforementioned adverse events in humans. In contrast an article by Ruffolo and Hieble on α-adrenoceptors notes that "α-adrenoceptors antagonists can inhibit catecholamine-induced ventricular arrhythmias in animals." No additional human data was provided.[1]

SELECTION OF CASES

Individual searches were conducted on November 15, 2001 using the Adverse Event Reporting System (AERS) for the drugs tamsulosin, terazosin, and doxazosin. AERS was searched using the MedDRA High Level Term "Ventricular Arrhythmias and Cardiac Arrest" and the Preferred Terms "Electrocardiogram QRS Complex Prolonged," "Electrocardiogram QT Corrected Interval Prolonged," "Electrocardiogram QT Prolonged," and "Torsade de Pointes." The search identified sixteen, fifty-four, and seventy-eight unduplicated cases for tamsulosin, terazosin, and doxazosin respectively.

1. Frishman WH and Kotob F. Alpha-adrenergic blocking drugs in clinical medicine. Journal of Clinical Pharmacology. 1999; 39:7-16.

Tamsulosin (n = 16)

Demographics

Age N = 16

Range	50 – 80 years		
Mean	67.75 years		
Median	65.5 years		
Sex	Male = 16		
Date of Event	1996 = 2	1997 = 2	1998 = 2
	1999 = 3	2000 = 2	2001 = 3
	Unknown = 2		
Report Location	Domestic = 5	Foreign = 11	
Outcome	Hospitalization = 7	Death = 7	Unknown = 2
Duration of Tamsulosin Treatment Range	2 hours – 3 years		

Two representative tamsulosin cases are presented below.

ISR# 3433020-4-00-01, MFG# 1999-003159, Foreign
A 76-year old male with a history of coronary artery disease was admitted to the hospital with "Torsade de Pointes associated with angina." The patient was also taking nifedipine, amitriptyline, Sinemet, isosorbide mononitrate, and acetylsalicylic acid. No outcome information is available.

ISR# 3103787-3-00, MFG# 1998-001665, Foreign
After taking tamsulosin for 10 days, a 62-year old male experienced atrial fibrillation with "tachycardic ventricular frequency." The patient collapsed and was treated with intravenous heparin, verapamil, and digitalis. Tamsulosin was discontinued. The patient recovered approximately 24 hours later. The patient had a history of chondrocalcinosis and hypomagnesemia. Concomitant medications were not reported.

Terazosin (n = 54)

Demographics				
Age	N = 48			
Range	25 – 84 years			
Mean	62.8 years			
Median	63.5 years			
Sex	Male = 41	Female = 10	Unknown = 3	
Date of Event	1987 = 1	1989 = 3	1990 = 4	1992 = 4
	1993 = 4	1994 = 9	1995 = 8	1996 = 3
	1997 = 2	1998 = 2	2001 = 1	Unknown = 13
Report Location	Domestic = 43	Foreign = 8	Unknown = 3	
Outcome	Recovered = 11	Death = 13	Hospitalization = 14	
	Unknown = 16			
Duration of Terazosin Treatment Range	<24 hours – 6 months			

Two representative terazosin cases are presented below.

ISR# 1511042, MFG# 62623, Domestic
A 40-year old male with no history of cardiac problems and no concomitant medications took terazosin for approximately two days and experienced a syncopal episode. The episode resulted in a cut under his eye which need stitches in the emergency room. He also received intravenous fluids during his ER stay. Upon rising in the emergency room the EKG monitor recorded ventricular trigeminy. The patient was monitored overnight in the emergency room and was discharged the next day without further treatment. Terazosin was discontinued at that time. The patient's physician indicates that no problems were identified during the patient's physical, which was completed approximately six months prior to the occurrence of the adverse event.

ISR# 688709, MFG# PCA50821 Domestic
A 59-year old male who was not taking any concomitant medications took a dose of terazosin 4-mg and experienced nasal congestion and dizziness. Later that night the patient was pale, sweaty, had no standing pulse or blood pressure and showed premature ventricular contractions on EKG. The patient was treated with intravenous fluids and the terazosin was discontinued. The patient recovered.

Doxazosin (n = 78)

Demographics				
Age	N = 64			
Range	26 – 90 years			
Mean	67.4 years			
Median	68.0 years			
Sex	Male = 55	Female = 7	Unknown = 16	
Date of Event	1990 = 2	1991 = 1	1992 = 3	1995 = 3
	1996 = 4	1997 = 2	1998 = 11	1999 = 17
	2000 = 18	2001 = 3	Unknown = 14	
Report Location	Domestic = 28	Foreign = 50		
Outcome	Hospitalization = 20	Death = 41	Required Intervention = 8	
	Other = 3	Unknown = 6		
Duration of Doxazosin Treatment Range	< 24 hours to 52 months			

Three representative doxazosin cases are presented below.

ISR# 3592622-5-00-1, MFG# A028871, Domestic
A 50-year old male took doxazosin (benign prostatic hypertrophy) for approximately three years without any noted adverse events. He also took tamsulosin. The patient started experiencing premature ventricular contractions (PVC). A cardiac work-up did not reveal any abnormalities. Doxazosin was discontinued and the PVCs stopped.

ISR# 3693804-4-00-01, MFG# A026513, Domestic
A 57-year old male took doxazosin for several years before palpitations started. Doxazosin was discontinued and the palpitations stopped. Doxazosin was restarted and the palpitations reoccurred. EKG results showed premature ventricular contractions and premature atrial contractions. The doxazosin was discontinued. The patient was also

taking hydrochlorothiazide, ranitidine, multivitamins, and receiving allergy shots. He was also on a low-fat diet and consumed approximately two ounces of alcohol on most days.

ISR# 3639263-9-00-01, MFG#A039989, Foreign
A literature report notes that a 79-year old female who was taking doxazosin, indapamide, and cisapride. She developed nausea and dizziness. The next day an ECG revealed that she had a prolonged QT interval. She developed ventricular extasystole, multiple ventricular tachycardia, and hypokalemia. Cisapride was discontinued and she was treated with magnesium and potassium. Her prolonged QT interval improved after treatment. She was also receiving amlodipine, aspirin, hydroxychloroquine, methotrexate, niacin, lansoprazole, and various multivitamins.

DISCUSSION

Seven deaths were identified in the tamsulosin group. Three of these cases involved (1) a patient who experienced chest pains and a respiratory infection for 3 weeks prior to seeking medical care, (2) a bronchitis/emphysema patient who chronically abused beta agonist inhalers, and (3) a patient who had received long-term treatment with haloperidol. The remaining four deaths involved patients with a prior history of cardiovascular problems—coronary heart disease, hypertension, hypercholesterolemia, and atheriosclerosis. Overall 10/16 cases (63%) involved patients who had a prior history of cardiovascular problems. Only one of the tamsulosin cases involved a patient who was admitted to the hospital with "Torsade de Pointes associated with angina." This patient had a history of coronary artery disease. However, limited data were provided for this case.

Although more cardiovascular adverse event terms were found when terazosin was used to treat benign prostatic hypertrophy, there were also quite a few cardiovascular terms for the hypertension indication (see table one). The most frequently noted adverse event terms found with terazosin were premature ventricular contractions, unspecified other cardiovascular events, death, cardiac arrest, ventricular tachycardia, syncope, and arrhythmia. Thirteen (24%) deaths occurred in the terazosin group. Six of the thirteen patients had a history of cardiovascular disease; two were taking medications that may have contributed to their deaths—Seldane and Clozaril—and the remaining five were not compelling cases. Twenty-six (48%) of 54 cases had a prior cardiovascular history (e.g., hypertension, coronary artery disease, hypercholesterolemia, etc). One patient in the terazosin category experienced Torsade de Pointes, but this case was confounded because the patient was also concomitantly taking Cisapride. Another patient experienced prolongation of the "Q interval." However, terazosin was discontinued 4 days prior to the occurrence of the cardiac events. The arrhythmia cases reported with terazosin were not compelling.

The majority of the adverse events reported with doxazosin were associated with the benign prostatic hypertrophy (BPH) indication (see table one). The most frequently noted adverse event terms found with doxazosin were ventricular tachycardia, cardiac arrest, and death. Although 40 BPH patients (51%) experienced cardiac arrests and/or death, 34 of these 40 patients (85%) were participating in the SINPMP Patient Compliance Program in Brazil. Seven of these deaths had a history of cardiovascular disease. No additional information is available for the patients in the SINPMP. Overall 25/78 patients had histories of cardiovascular disease that may have contributed to the adverse event. One case involved QT prolongation. However, the patient was also taking Cisapride. The arrhythmia cases were not compelling and involved patients who were "quite ill," in hypertensive crisis, or had prior ventricular arrhythmias.

Table One
Cardiovascular-Related Adverse Event Terms Reported for Terazosin and Doxazosin
(More than one term may be present in each case)

Terazosin Adverse Event Terms					*Doxazosin Adverse Event Terms*				
Adverse Event	*BPH*	*HTN*	*BPH & HTN*	*Unknown*	*Adverse Event*	*BPH*	*HTN*	*BPH & HTN*	*Unknown*
Arrhythmia (unspecified)	2	3			Arrhythmia (unspecified)	2		1	1
Cardiovascular Accident					Cardiovascular Accident	2			
Cardiac Arrest	1	2		3	Cardiac Arrest	40	1		1
Death (Cardiac)	3	4	2	2	Death (Cardiac)	40			1
Hypertensive Crises					Hypertensive Crises		1		
Other Cardiovascular	8	4	2	1	Other Cardiovascular	3	1		1
Palpitations	3	1			Palpitations	1	1		2
Premature Ventricular Contractions	9	6	2	2	Premature Ventricular Contractions	6		1	2
QT Prolongation	1				QT Prolongation	1			
Syncope	3	1		2	Syncope	2	2		
Torsade de Pointes		1			Torsade de Pointes				
Ventricular Tachycardia	3	2	2	1	Ventricular Tachycardia	9			1
Ventricular Fibrillation	2				Ventricular Fibrillation	3			
Totals	**35**	**24**	**8**	**11**	**Totals**	**109**	**6**	**2**	**9**