CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-434

Administrative/Correspondence

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-434 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 12/26/01 Action Date: 1/21/03

HFD 120 Trade and generic names/dosage form: Xanax XR (alprazolam) Extended-release Tablets

Applicant: Pharmacia Therapeutic Class: 3S

Indication(s) previously approved: n/a

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: panic disorder

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: X Partial Waiver X Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr. < 13	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 13	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 17	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 1/31/06

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Anna-Marie Homonnay
1/14/03 09:50:44 AM

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ON ORIGINAL

MEMORANDUM

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

DATE: January 15 , 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Xanax XR (alprazolam extended release) for the treatment of panic disorder, with or without agoraphobia

TO: File NDA 21-434
[**Note:** This overview should be filed with the 11-20-02 response to our 10-25-02 approvable letter.]

In our 10-25-02 approvable letter, we asked that the following issues be addressed before final approval: (1) exploration for effective dose range in positive studies; (2) support for bid dosing regimen; (3) safety update; (4) regulatory status update; (5) literature update; (6) CMC deficiencies; (7) ethnicity and pharmacokinetics; (8) concerns about container and carton labeling. In addition, we provided draft labeling.

In their 10-25-02 response, the sponsor fully addressed all of these concerns. These responses were reviewed by: (1) Robert Levin, M.D., from the clinical group; (2) Lorenzo Rocco, Ph.D., from the chemistry group; and (3) Wendy Chou, Ph.D., from OCPB.

Exploration for Effective Dose Range in Positive Studies

-The two positive studies supporting the approval of Xanax XR were flexible dose studies, including a range of 1 to 10 mg/day. In addition, there were two negative fixed dose studies, including fixed doses of [redacted] nd 6 mg/day. In order to address the concern raised by the negative studies at th[redacted] 6 mg/day dose range [redacted] (based on mean doses in the flexible dose trials), we asked the sponsor to do additional exploratory work with studies 369 and 271 in order to try to better understand which doses appeared to be the effective doses in those trials.

-Sponsor Analyses and Findings: The sponsor pooled the data from studies 369 and 271 (n=332), and characterized patients based on the last dose taken. They then provided descriptive statistics for each of the 7 primary endpoints, by each of the 10 doses (1 through 10 mg), and placebo. There were n=161 placebo patients and n=171 Xanax XR patients. Slightly over half of patients (93/171 = 54%) were categorized as 3 to 6 mg patients, and the sponsor focused on this subgroup, comparing the effect

size for these 4 dose groups with placebo and the 10 combined Xanax XR groups. For almost all comparisons across the 7 outcomes, these 4 groups were numerically superior to placebo and at least as good as the combination of all 10 groups. The sponsor concluded that this was a reasonable target dose range, based on these analyses.

-Comment: The 1 and 2 mg doses also generally beat placebo numerically, as did most of the doses higher than 6 mg. However, the 1 and 2 mg dose groups were generally not as numerically robust as the 3 to 6 mg doses, nor was there any clear advantage to higher doses over the 3 to 6 mg doses. Thus, I agree that it is not unreasonable to target 3 to 6 mg, especially since the proposed labeling language encourages 0.5 to 1 mg as a starting dose, with gradual increases until efficacy is established. Presumably clinicians would stop if efficacy is established at 1 or 2 mg in an individual patient.

Support for BID Dosing Regimen

-Although the sponsor did not provide data from clinical trials supporting a bid dosing regimen for Xanax XR (Note: all of their efficacy trials involved qd dosing), they [redacted] with pharmacokinetic data [redacted] with data showing that the range of plasma levels achieved (Cmax and Cmin) during a day with twice a day dosing was approximately the same as the range of plasma levels achieved with Xanax XR given qd and Xanax IR given qid. In fact, we had informed them in earlier discussions that plasma levels achieved with Xanax XR bid must fall between the levels achieved with the XR given qd and the IR given qid, at all time points during the day. Since they were not able to demonstrate this outcome, we asked that [redacted]

-The sponsor has chosen [redacted] has accepted labeling that recommends only qd dosing with Xanax XR.

Support for a Statement in Labeling on Switching Patients from Xanax IR to Xanax XR

-The sponsor has taken this opportunity to add new language to D&A regarding the switch from Xanax IR to XR. Their language advises clinicians to switch patients to the same total dose of XR as they were taking IR. They base this language on an analysis of the data from study 271 (IR, XR, Pbo) that is very similar to the analysis done to support the 3-6 mg/day dose range. Their analysis compares (for IR vs XR) the effect sizes for each of the 10 dose groups vs placebo. They conclude that similar efficacy is demonstrated for the IR and XR at the same total daily dose, especially in the 3 to 6 mg/day dose range.

-Comment: This is, again, a somewhat rough numerical analysis, however, I agree that it is probably sufficient to support this switching language, especially since the language provides for further titration if the equal dose switch is unsuccessful.

Safety Update

-Xanax XR was first introduced in a nonUS country in August, 1994, and this NDA included findings from the sponsor's postmarketing database from August, 1994 through November, 2001. The 120-day safety update included findings from 11-6-01 through 4-15-02. In preparation for this resubmission of the NDA, this database was search for the period of 4-16-02 through 10-31-02 for serious adverse events, and none were found. There were no additional clinical trials with Xanax XR conducted during this period.

Regulatory Status Update
-Xanax XR was already approved in more than 50 countries at the time of the submission of the NDA, and it has been approved in one additional country as of 12-26-02.

Literature Update
-The original NDA included a literature search covering a period from 1989 through August, 1991. The 120-day safety update included a literature search from September, 2001 through 4-15-02. For this resubmission, a search was conducted for the period from 4-16-02 through 10-31-02. No additional alprazolam XR publications were found.

CMC Deficiencies
-It is my impression that all remaining CMC deficiencies have been addressed at this point.

Ethnicity and Pharmacokinetics
-In the approvable letter, we had asked for an update on ethnicity, pharmacokinetics, and safety/efficacy outcomes, from the literature and/or postmarketing surveillance. The sponsor has proposed a brief summary statement regarding slight increases in concentration and half-life in Asians vs Caucasians.

-Comment: OCPB has accepted this response.

Concerns about Container and Carton Labeling
-It is my impression that all concerns about container and carton labeling have been addressed at this point.

Final Labeling
-We have reached agreement with the sponsor regarding final labeling as of 1-15-03.
-As noted, they accepted labeling that recommends only qd dosing.
-They have also accepted our deletion of language suggesting [redacted]

-They have largely rewritten the D&A section, now targeting 3-6 mg, and they have added language regarding the switch from IR to XR. I agree with this revised section.

Conclusions and Recommendations

I believe that Pharmacia and Upjohn have submitted sufficient data to support the conclusion that Xanax XR is effective and acceptably safe in the treatment of panic disorder. I recommend that we issue the attached approval letter along with the mutually agreed upon final labeling.

cc:
Orig NDA 21-434
HFD-120
HFD-120/TLaughren/RKatz/RLevin/MShin/AHomonnay

DOC: MEMXXRPD.AP1

APPEARS THIS WAY
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/s/

Thomas Laughren
1/15/03 12:15:03 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Review of Sponsor's Response to Approvable Letter

Sponsor:	Pharmacia
Drug:	XANAX XR (alprazolam extended release)
Material Submitted:	Response to Approvable Letter (N-BZ)
Correspondence Date:	November 20, 2002
Date Received:	November 21, 2002
Drug Category:	Benzodiazepine; Anxiolytic
Forms available for proposed study:	0.5 mg, 1 mg, 2 mg, and 3 mg tabs
Related INDs:	— 23,179

I. Background

In this submission, the sponsor has responded to the Division's Approvable Letter dated October 25, 2002. The Division had requested that the sponsor address several key issues including: 1) proposed labeling; and 2) potential dose-response relationships with XANAX XR. In addition, the submission addresses biopharmaceutic and CMC issues, and it contains Regulatory Status, World Literature, and Safety updates. The sponsor has also included proposed labeling regarding strategies for switching patients from XANAX IR to XANAX IR treatment.

II. Summary of Findings and Conclusions

A. Dose-Response Relationship for XANAX XR

The sponsor has provided useful information, which suggests that there was a relatively flat relationship between XANAX XR doses and subjects' mean responses (as measured by 7 co-primary efficacy measures) over most of the dosing range. Subgroups of subjects responded to each individual dose level within the dosing range of 1-10 mg. The majority of responders (~60%) reached final effective dosages which were in the range of 2-6 mg. Within this dose range, there was no evidence of an increasing response rate at successively higher doses. Because the numbers of responders with final effective doses of 1, 7, 8, 9, and 10 mg were small, it is difficult to interpret the dose-response data for these doses; however, the levels of

response at these doses appear to approximate response levels observed with other doses.

Since the study employed flexible dosing, it was not ideally designed to assess potential dose-response relationships. Nevertheless, the data support the conclusion that the study was positive based on the presence of responders throughout the complete flexible dosing range, as opposed to demonstrating efficacy primarily due to responses at higher doses ($\geq$ 7 mg).

B. Proposed Labeling Changes

In summary, the labeling changes proposed by the sponsor are reasonable, they thoroughly address potential safety concerns, and they accurately reflect the results of the XANAX XR clinical studies under review. The Division does not recommend further amendments at this point. Pertinent labeling sections include the following:
1) Clinical Pharmacokinetics; 2) CLINICAL EFFICACY TRIALS; 3) Interdose Symptoms; 4) ADVERSE REACTIONS; and 5) DOSAGE AND ADMINISTRATION.

Of note, in contrast to previous versions of proposed labeling, here the sponsor does not seek labeling for the use [redacted]

C. Switching Treatment from XANAX IR to XANAX XR

Essentially, the sponsor recommends that in switching a patient from XANAX IR to XANAX XR, the physician should initiate the change by substituting the total daily XANAX IR dose with a single daily dose of XANAX XR. The sponsor suggests that: "If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above [in the DOSAGE AND ADMINISTRATION section]."

Proposed labeling is reasonable, based on the finding from **Study 271** that the dose-response relationships of XANAX IR and XANAX IR appear to be approximately equivalent. As above, there are limits on the degree to which one can interpret the type of dose-response data provided. In any case, the sponsor's recommended switching strategy appears to be the safest and most rational approach in guiding prescribers who choose to change a patient's treatment from XANAX IR to XANAX XR.

D. Regulatory Status Update
Since the submission of NDA 21,434 on December 26, 2001, there has been one additional approval for registration (Kazakhstan, May 24, 2002). XANAX XR has never been refused approval for safety reasons.

E. World Literature Update
Since the last submission, there have been no additional publications pertaining to XANAX XR.

F. Safety Update
The sponsor's spontaneous adverse event database was reviewed for the period of April 16, 2002 through October 31, 2002 for serious adverse events that were reported in association with use of alprazolam XR. There were no serious adverse events reported for this time period.

G. Biopharmaceutic and CMC Issues
These items will be addressed by reviewers in the respective disciplines.

III. Conclusions and Recommendations
The sponsor has adequately addressed all of the items that the Division specified in the Approvable Letter. I recommend that the Division accept the proposed labeling changes and take an approvable action for NDA 21,434.

S 12-13-02

Robert Levin, M.D., December 13, 2002
Medical Reviewer
FDA CDER ODE1 DNDP HFD 120

cc: IHFD 120
R Levin
A Hommonay-Weikel
T Laughren

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

/s/

Robert Levin
12/13/02 03:29:59 PM
MEDICAL OFFICER

Thomas Laughren
12/13/02 03:43:16 PM
MEDICAL OFFICER
This NDA can be approved once the remaining CMC and biopharm issues are resolved; see memo to file for more detailed comments.--TPL

M E M O R A N D U M

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

DATE: October 16, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Xanax XR (alprazolam extended release) for the treatment of panic disorder, with or without agoraphobia

TO: File NDA 21-434
[**Note:** This overview should be filed with the 12-26-01 original submission.]

1.0 BACKGROUND

Alprazolam is a triazolobenzodiazepine that is currently approved and marketed as Xanax, an immediate release form for the treatment of generalized anxiety disorder and also for panic disorder, with or without agoraphobia. Xanax XR is an extended release form of alprazolam, proposed for use in the treatment of panic disorder. Xanax IR is generally given on a tid or even qid basis. The rationale for Xanax XR is improved convenience and compliance, due to the need for less frequent dosing. Thus, the sponsor has proposed that Xanax XR be given on a qd [redacted] beginning at 0.5 to 1 mg/day, with gradual titration, at intervals of 3-4 days in increments of no more than 1 mg/day, up to 4 mg/day for most patients. As with Xanax, Xanax XR labeling indicates that occasional patients may need doses up to 10 mg/day. Xanax XR is being proposed for use in the following strengths: 0.5, 1, 2, and 3 mg.

There are presently several other drugs approved for the treatment of panic disorder, including clonazepam, another benzodiazepine, and three SSRIs: sertraline, fluoxetine, and paroxetine.

[redacted] This NDA included results from one positive clinical study in panic disorder, along with PK data. During the course of the review of that NDA, DNDP policy changed to require two positive clinical trials for an extended release form of a drug already approved in an immediate release form.

We held a preNDA meeting with PNU on 7-19-01. The sponsor was primarily interested in finding out if, at this point in time, DNDP policy would now permit an approval of Xanax XR with only one positive clinical study, along with PK and safety data. We indicated that this was now accepted policy. Several additional points were made:

-Since the one positive clinical study involved qd dosing, labeling for bid dosing would require a demonstration that the time-concentration profile for bid dosing would fall between those for qd dosing with Xanax XR and qid dosing with Xanax IR.

Studies in support of this claim were conducted under IND 23,179.

The currently pending NDA for Xanax XR was submitted 12-26-01. A filing meeting was held on 2-13-02, and the application was considered fileable.

The CMC review of this NDA was conducted by Lorenzo Rocco, Ph.D., from chemistry. The pharm/tox review of this NDA, which was limited to proposed labeling changes, was conducted by Aisar Atrakchi, Ph.D., from pharmacology. The biopharmaceutics review of this NDA was conducted by Wen-Hwei Chou, Ph.D., from OCPB. The primary review of the efficacy and safety data was done by Robert Levin, M.D., from the clinical group. Fanhui Kong, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

The chemistry review was not completed at the time of finalizing this memo. However, I am not aware of any CMC issues that would preclude an approvable action for this NDA.

3.0 PHARMACOLOGY

As noted, the only pharmacology issues requiring review were two proposed modifications to labeling: from the overdose section; There was no objection to removing the from the overdose section, since there is extensive human experience at this point. However, we do not agree with the deletion of information about cataract induction The sponsor had argued that this information is no longer relevant, given the years of experience in humans. However, the sponsor has provided no evidence for any systematic exploration for this finding, and spontaneous report is not likely to be an effective approach to detecting an excess for this common background event.

4.0 BIOPHARMACEUTICS

Xanax XR has similar pharmacokinetics to Xanax IR, except for slower absorption, resulting in a relatively constant level over a 5 to 11 hour interval. The one positive study with Xanax XR supporting this approval used qd dosing,

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Results from a total of five placebo-controlled efficacy trials of Xanax XR in panic disorder were submitted in this NDA, however, there was agreement that, on face, only one of these trials was positive on the primary outcomes. Thus, the clinical and statistical reviewers focused on the detailed results of that one study, i.e., study M/2000/0369. As noted, we had reached prior agreement with the sponsor that one positive efficacy study would suffice as support for approval. I will also focus on the results of study 369, however, I will comment briefly on three of the other placebo-conrolled studies, since their outcomes do bear somewhat on the overall approval decision and particularly on the question of whether or not their negative results should be described in labeling. The fourth other placebo-controlled study (M/2002/0032) was a small, pilot study involving adjunctive Xanax XR treatment in patients receiving cognitive-behavior therapy, and is not relevant from the standpoint of efficacy.

5.1.2 Summary of Study 369

This was a randomized, double-blind, parallel group, 6-week, flexible-dose, multicenter (3 US sites) study comparing Xanax XR, in a dose range of 1 to 10 mg/day, on a qd schedule, and placebo, in adult outpatients (18-65) meeting DSM-III criteria for panic disorder, with or without agoraphobia. Randomization was preceded by a 7-day open run-in. Treatment was initiated at 1 mg/day, and gradually titrated upward, based on response and tolerability, to a maximum dose of 10 mg/day.

Seven co-primary endpoints were designated in the protocol: (1) 3 measures of panic attack frequency: (a) mean change from baseline; (b) proportion of patients with $\geq$ 50% decrease from baseline; (c) proportion of patients with zero panic attacks; (2) 3 measures of the CGI: (a) CGI-Severity; (b) CGI-Improvement; (c) CGI-Efficacy Index (a measure that combines efficacy and side effects); (3) mean change from baseline in Overall Phobia Scale. Efficacy assessments were obtained

at baseline and weekly during the six weeks of the study. There were also numerous secondary endpoints. The primary analysis model was ANOVA with treatment and investigator as main effects, using LOCF in our usual intent-to-treat population (all randomized patients who received at least one dose of assigned treatment, and had baseline and at least one followup visit for efficacy assessment).

There were n=199 patients in the ITT sample (n=95 for pbo and n=104 for Xanax XR). There were substantial dropouts before reaching the 6 week endpoint, with the % completing to 6 weeks ranging from 54% for placebo to 74% for Xanax XR (for ITT population). The patients were about 60% female, about 96% Caucasian, and the mean age was about 35 years. The daily Xanax XR dose for completers peaked in the 5th week, with a mean dose of approximately 5 mg.

Efficacy Results on 7 Primary Endpoints (LOCF at Week 6 for ITT) for Study 0369			
Endpoint	Xanax XR	Placebo	P-Value
Total Panic Attacks			
Mean change-BL	-4.7	-2.0	0.026
% ≥50% decres-BL	84%	62%	< 0.001
% achieved zero	70%	45%	< 0.001
CGI			
CGI-S/Change-BL	-2.0	-1.0	0.0001
CGI-I	2.0	3.1	0.0001
Efficacy Index	4.2	3.2	0.0001
Overall Phobia Scale			
Mean change-BL	-3.6	-2.2	0.0028

Most of the OC analyses also favored Xanax XR over placebo for the primary endpoints, as did the analyses of many secondary outcomes. Dr. Kong also performed nonparametric analyses on the primary endpoints, given his concern about a failure of the normality assumption, and the results still favored Xanax XR over placebo.

All 3 sites were inspected, and revealed in one of the 3 sites (Rosenthal) an absence of source documents for 28 of 37 patients. A re-analysis without Rosenthal's data resulted in generally even smaller p-values.

Dr. Kong performed several subgroup analyses. An evaluation by investigator revealed consistent findings favoring Xanax XR for both acceptable sites. There were too few elderly or non-white

patients to do age or race subgroup analyses, however, an analysis by gender showed positive results for Xanax XR in both strata.

Dr. Kong expressed concern about the unusual number of early dropouts, apparently mostly for failure to return for the second visit (12 for drug and 5 for placebo). To test for possible bias, he compared the pattern of changes in efficacy measures for dropouts and non-dropouts, and found no difference. Thus, the somewhat less impressive results on OC analyses probably represented diminished power.

Comment: Both Drs. Levin and Kong considered this a positive study, and I agree.

5.1.3 Summary of Study M/2000/0271

This was a randomized, double-blind, parallel group, 6-week, flexible-dose, multicenter (3 US and Canadian sites) study comparing Xanax XR, in a dose range of 1 to 10 mg/day, on a qd schedule, Xanax tablets (the marketed tablet), in a dose range of 1 to 10 mg/day, on a qid schedule, and placebo, in adult outpatients (18-65) meeting DSM-III criteria for panic disorder, with or without agoraphobia. The design of this study was very similar to that for 369, with identidal primary endpoints. The ITT population included roughly 70 patients per group. Both forms of Xanax were superior to placebo on all 3 CGI measures, on the Overall Phobia State measure, and on the proportions of patients with $\geq$ 50% reduction from baseline in total panic attacks. However, neither group beat placebo on mean change from baseline in total panic attacks, and only the Xanax tablets beat placebo on the proportions of patients with 0 panic attacks at endpoint.

Comment: Drs.Levin and Kong considered this a supportive study, but not a positive study, and I agree. Given that neither active drug was shown to be superior to placebo, I consider this a failed study that does not need to be described in labeling.

5.1.3 Summary of Study M/2002/0003

This was a randomized, double-blind, parallel group, 8-week, fixed-dose, multicenter (16 US sites) study comparing Xanax XR, at doses of 4 and 6 mg/day, on a qd schedule, and placebo, in adult outpatients (18-65) meeting DSM-III criteria for panic disorder, with or without agoraphobia. There were 5 primary endpoints: change from baseline in total number of panic attacks; proportions of patients with zero panic attacks at endpoint; change from baseline in CGI-S; CGI-I; and change from baseline in Overall Phobia State. The ITT population included roughly 90 patients per group. The results of this study were uniformly negative, for both dose groups, and for all 5 primary endpoints.

Comment: Drs. Levin and Kong considered this a negative, and I agree.

5.1.3 Summary of Study M/2002/0002

This was a randomized, double-blind, parallel group, 8-week, fixed-dose, multicenter (15 US sites) study comparing Xanax XR, at doses of 4 and 6 mg/day, on a qd schedule, and placebo, in adult outpatients (18-65) meeting DSM-III criteria for panic disorder, with or without agoraphobia. There were 5 primary endpoints: change from baseline in total number of panic attacks; proportions of

patients with zero panic attacks at endpoint; change from baseline in CGI-S; CGI-I; and change from baseline in Overall Phobia State. The ITT population included roughly 75 patients per group. The results of this study were uniformly negative, for both dose groups, and for all 5 primary endpoints.

Comment: Drs. Levin and Kong considered this a negative, and I agree.

5.1.4 Comment on Other Important Clinical Issues

Evidence Bearing on the Question of Dose/Response for Efficacy

There were no data in this program that contribute useful information to the question of dose response for effectiveness. Labeling will simply describe how patients were dosed in the one positive trial.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, and these analyses suggested treatment effects in both strata.

Size of Treatment Effect

The effect size as measured by difference between drug and placebo in change from baseline on the 7 primary endpoints in study 369 was similar to that seen in the positive trials for other drugs approved for panic disorder. I consider this a sufficient effect to support a claim for this product in panic disorder.

Duration of Treatment

There were no data presented in this program pertinent to the question of the longer-term efficacy of Xanax XR in panic disorder.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy for Xanax XR in panic disorder.

5.2 Safety Data

Dr. Levin's safety review of this NDA was based predominantly on the safety data from the 5 placebo-controlled studies conducted in patients with panic disorder for this program. There were n=531 panic disorder patients exposed to Xanax XR across these 5 studies, representing about 62 patient years of exposure. The majority of patients treated with Xanax XR in these trials (81%) received mean daily doses in a range of 2 to 6 mg. Any SAEs were also examined from the entire

Xanax XR exposed-population in this NDA, i.e., a total of n=1564. These exposures came from a total of 24 phase 1 studies (n=598 Xanax XR exposures) and 13 phase 2-3 studies (n=966 Xanax XR exposures). There were no deaths in this development program

Given our prior knowledge of the risks associated with Xanax IR in the two populations for which this drug is approved, the focus in the safety review was on any differences between the recognized safety profile with the IR formulation with that observed for Xanax XR in patients with panic disorder.

5.2.1 Overview of Adverse Event Profile for Xanax XR in Panic Disorder

Overall, the adverse events profile for Xanax XR in the panic disorder population was similar to that observed for Xanax IR. Of note, the most commonly reported treatment-emergent adverse events for Xanax XR were sedation, somnolence, memory impairment, fatigue, depression, dysarthria, impaired coordination, cognitive impairment, ataxia, and decreased libido. The most commonly reported discontinuation-emergent adverse events for Xanax XR were anxiety, tremor, dizziness, headache, insomnia, depression, decreased appetite, hyperventilation, and derealization. It should be noted that all 5 of the placebo-controlled phase 2-3 clinical studies in panic disorder included long periods of tapering and withdrawal from Xanax XR (5-6 weeks). This development program included reports for studies comparing abuse liability of Xanax XR, Xanax IR, and several other benzodiazepines on "liking" measures among subjects with histories of sedative/hypnotic abuse. The sponsor's conclusion from the liking studies was that Xanax XR falls between Xanax IR and placebo, and on this basis, they have proposed language in labeling declaring this advantage.
Comment: I think these studies may be inadequate to support such a claim, and I have asked that these data be sent to CSS for a consult.

5.2.2 Conclusions Regarding Safety of Xanax XR in Panic Disorder

There were no new safety findings to suggest a different safety profile for Xanax XR in panic disorder compared to that seen with Xanax IR.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

The sponsor provided a literature review focused on Xanax XR and panic disorder. Dr. Levin examined a review of this literature provided by the sponsor and indicated that it revealed no new safety findings that would impact on the labeling of Xanax XR. He also conducted a somewhat more limited independent literature review and reached a similar conclusion.

7.0 FOREIGN REGULATORY ACTIONS

Xanax XR is approved for use in 51 countries, for indications including panic disorder, among a variety of other disorders. It has never been refused approval for safety reasons, or removed from marketing for safety reasons. We will ask for an update on the regulatory status of Xanax XR for the treatment of panic disorder in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

As noted above, all 3 sites for study 369 were inspected, with positive findings at one site that led to a re-analysis without the data from that site (see efficacy above).

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 12-26-01.

10.2 Foreign Labeling

No foreign labeling was included with this NDA; we will ask for this in the approvable letter.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pharmacia and Upjohn have submitted sufficient data to support the conclusion that Xanax XR is effective and acceptably safe in the treatment of panic disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 21-434
HFD-120
HFD-120/TLaughren/RKatz/RLevin/MShin/AHomonnay

DOC: MEMXXRPD.AE1

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/

Thomas Laughren
10/16/02 12:32:39 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE

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

DATE RECEIVED: April 26, 2002	DUE DATE: September 6, 2002	ODS CONSULT #: 02-0080

TO: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Melaine Shin
Project Manager
HFD-120

PRODUCT NAME:	NDA SPONSOR:
Xanax XR (Alprazolam Extended-release Tablets) 0.5 mg, 1 mg, 2 mg, and 3 mg NDA#: 21-434	Pharmacia and Upjohn

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Xanax XR" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objections to the use of the proprietary name, Xanax XR. However, DMETS recommends implementing the labeling revisions outlined in Section III of this review, in order to minimize potential errors with the use of this product.

This name, along with its associated labels and labeling, 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 or established names from the signature date of this document.

/S/ /S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
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; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 6, 2002

NDA#: 21-434

NAME OF DRUG: Xanax XR (Alprazolam Extended-release Tablets) 0.5 mg, 1 mg, 2 mg, and 3 mg

NDA HOLDER: Pharmacia and Upjohn

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the tradename "Xanax XR," regarding potential name confusion with other proprietary drug names. The container labels, carton labeling and package insert labeling for Xanax XR were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Pharmacia and Upjohn currently markets Xanax in an immediate release tablet formulation in 0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths. Xanax XR contains the same active ingredient as Xanax (alprazolam) but is formulated as an extended-release tablet.

Xanax XR is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds. Xanax XR is an extended-release tablet for oral administration, available as 0.5 mg, 1 mg, 2 mg, and 3 mg tablets. The tablet should not be crushed or chewed during administration. Although the immediate release Xanax product is indicated for the treatment of anxiety and/or panic disorders, Xanax XR is only indicated for the treatment of panic disorders, with or without agoraphobia. The recommended dosing interval for Xanax XR is once daily. However, Xanax XR may be given
The dose of Xanax XR must be individualized for maximum benefit. Most patients will be managed with
. Xanax XR will be supplied in bottles of 60,
tablets.

II. RISK ASSESSMENT:

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Xanax" has been utilized in the U.S. marketplace since October 1981. A search

was conducted 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 Xanax XR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. Searches 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. Since the proprietary name Xanax has been approved for more than twenty years, the standard DMETS prescription analysis studies were not conducted.

The FDA Adverse Event Reporting System (AERS) was searched for any postmarketing safety reports of medication errors associated with the name Xanax. AERS was also searched for postmarketing safety reports of medication errors associated with the modifier 'XR.'

A. REFERENCE SEARCH

The search of the reference texts and databases did not identify any sound-alike or look-alike names of concern.

DDMAC did not have concerns about the name Xanax XR with regard to promotional claims.

B. AERS DATABASE SEARCHES

The Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with Xanax. The MEDDRA Preferred Term (PT) "Medication Error" and the terms "Xanax," "Alprazolam," "Alpra%," and "Xan%" were used as search criteria. The search identified forty-seven reports but none of the reports involved name confusion with Xanax.

The electronic Orange Book was searched for all approved products that contain the modifier 'XR.' This search yielded the following products: Adderall XR, Dilacor XR, Effexor XR, Glucophage XR, Tegretol XR, and Voltaren XR. The AERS database was searched using the Preferred Term "Medication Error" and the proprietary and established name of each aforementioned product. Sixty-nine reports were identified. Of these reports, eight cases involved confusion with the modifier "XR."

C. SAFETY EVALUATOR RISK ASSESSMENT

A search of the AERS database did not identify any medication error reports involving name confusion with Xanax. Therefore, there is no evidence at this time to conclude that the proprietary name, Xanax, has significant potential for name confusion. DMETS will

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

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

continue to monitor postmarketing medication errors in association with the proprietary name, Xanax.

'XR' is currently used as a modifier for several extended-release products (Adderall XR, Dilacor XR, Effexor XR, Glucophage XR Tegretol XR, and Voltaren XR). For these products, the modifier 'XR' is used to differentiate the extended-release products from their corresponding immediate release formulation [e.g., Effexor XR vs. Effexor (immediate release)]. The modifier 'XR' is used with Xanax to differentiate the extended release product from the immediate release product. The majority of the aforementioned extended-release products have a recommended dosing interval of once a day. Tegretol XR is the only product with a twice a day dosing interval. The recommended dosing interval for Xanax XR is also once a day, although some patients may benefit from twice daily dosing. Based on the once-a-day dosing interval and the need to differentiate the extended release formulation from the immediate release formulation, use of the modifier 'XR' would be appropriate to identify the product Xanax XR.

The search of the Adverse Events Reporting System identified eight cases associated with confusion with the modifier 'XR.' Five cases for Effexor/Effexor XR, two cases for Glucophage/Glucophage XR, and one case with Adderall/Adderall XR. See Attachment One for details of the eight cases. In all eight cases confusion between the overlapping strengths of the immediate release and extended release products contributed to the medication error. Table One shows the overlapping strengths between the immediate release and the extended release products.

Table One

	Available Immediate Release Strengths (mg)	Available 'XR' Extended Release Strengths (mg)
Adderall	5 mg, 7.5 mg, 10 mg, 12.5 mg, 20 mg, 30 mg	5 mg, 10 mg, 15 mg 20 mg, 25 mg, 30 mg
Voltaren	25, 50, 75	100
Tegretol	100, 200	100, 200, 400
Effexor	25, 37.5, 50, 75, 150	37.5, 75, 150
Glucophage	500, 850, 1000	500
Dilacor	N/A	120 mg, 180 mg, 240 mg

Denotes overlapping strengths between immediate release and extended release

In six of the eight AERS cases the pharmacist filled either a new or refill prescription with the incorrect formulation (e.g., Effexor XR 75 mg intended, but filled with Effexor 75 mg). The two remaining cases involved physicians. One physician dispensed samples of Effexor XR in lieu of Effexor and the second physician "ordered [Glucophage] the new drug but forgot to mention XR form." In all eight cases, overlapping strengths may have contributed to the medication errors. Xanax is available in 0.25 mg, 0.5 mg, 1 mg, and 2 mg strengths while Xanax XR is available in 0.5 mg, 1 mg, 2 mg, and 3 mg strengths. Overlapping strengths (i.e., 0.5 mg, 1 mg, and 2 mg) may increase the potential risk of medication errors between the immediate and extended release formulations of Xanax. DMETS is concerned that patients may interchange the Xanax XR formulation with the Xanax immediate release formulation since some of the product strengths overlap. Additionally, pharmacy dispensing errors may occur, especially during the launch period, as a result of the overlapping strengths.

DMETS is also concerned with the potential consequences of a medication error if a prescription for Xanax is filled with Xanax XR and vice versa. Patients who receive Xanax in lieu of Xanax XR may experience reappearance of their symptoms prematurely because the dosing interval of Xanax's immediate release formulation is more frequent than the once a day dosing interval of Xanax XR. Thus the duration of effect of the once-a-day tablet will be longer than the immediate release tablet. The other scenario is that a patient might receive Xanax XR instead of Xanax (e.g., Xanax 1 mg TID filled with Xanax XR 1 mg TID). The proposed package insert indicates that the bioavailability and pharmacokinetics of alprazolam following both Xanax and Xanax XR administration is the same except for the rate of absorption and the peak plasma concentration. Administration of Xanax XR tablets results in a slower rate of absorption and decreased peak plasma concentration levels (which occur in 5-11 hours vs. 1-2 hours for Xanax). The labeling also contains a statement indicating that steady-state peak and trough concentrations for equivalent doses of Xanax XR every 12 hours and Xanax four times a day are the same. Based on the data provided, DMETS cannot determine the clinical effect a switch, as listed above, would have on a patient. Although patients would still receive equal amounts of alprazolam (e.g., 1 mg extended release vs. 1 mg immediate release), DMETS is unsure if the effects of the extended release formulation will contribute to an increase in adverse events such as sedation, somnolence, and memory impairment.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Xanax XR, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has reviewed the current container labels, carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Revise the established name to read "Alprazolam Extended-release Tablets." Additionally, increase the prominence of the established name so that it is at least half as large as the proprietary name.

2. DMETS acknowledges the sponsor's attempt to distinguish the proprietary name, Xanax XR from Xanax by placing the modifier 'XR' in a contrasting background. However, the current presentation of the modifier does not necessarily help to distinguish the two products. The current presentation of 'XR' looks similar to a logo and thus, it may not help to distinguish the product. We recommend that the format (font, color, and background contrast) of the modifier 'XR' be the same as the format of the proprietary name.

3. DMETS recommends that each strength of the immediate release and extended release formulations be distinguished by a different color. This differentiation may help to decrease selection errors between the two formulations and is particularly important in the 0.5 mg, 1 mg, and 2 mg strengths, since the two formulations have overlapping strengths. [In the current presentation, the strength (0.5 mg) on the carton labeling for Xanax and Xanax XR is presented in the same color (i.e., green).]

V. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Xanax XR.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling 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 or established names from this date forward.

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

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/

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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ON ORIGINAL

Attachment One

	Source AERS	Date of Event/ Report	Intended Product	Dispensed Product	Outcome/Description
1	3208763-8 (USP 52081)	2/10/99	Effexor XR 75 mg	Effexor 75 mg	Actual Error. A prescription for Effexor XR 75 mg was dispensed with Effexor 75 mg. The patient discovered the error prior to ingestion.
2	3332283-3	3/99	Effexor 75 mg	Effexor XR 75 mg	Actual Error. A patient received Effexor XR 75 mg instead of Effexor 75 mg. She experienced dizziness, diarrhea, and fell down without any muscle coordination.
3	3332288-2	5/4/99	Effexor 150 mg	Effexor XR 150 mg	Actual Error. A patient received Effexor XR 150 mg instead of Effexor 150 mg. She took Effexor XR 600 mg daily for an unknown amount of time.
4	3460522-7	4/13/99	Effexor XR 150 mg	Effexor 150 mg	Actual Error. A patient received Effexor 150 mg instead of Effexor XR 150 mg. Within a week of taking Effexor 300 mg daily, she experienced increased blood pressure.
5	3762570-6	6/11/01	Effexor 37.5 mg	Effexor XR 37.5 mg	Actual Error. A physician dispensed samples of Effexor XR 37.5 mg instead of Effexor 37.5 mg. The error was discovered prior to ingestion
6	3824270-3 (USP 54575)	10/25/01	Glucophage XR 500 mg	Glucophage 500 mg	Actual Error. A refill for Glucophage XR 500 mg was filled with Glucophage 500 mg. A patient discovered the error prior to ingestion.
7	3895548-2 (USP 54804)	3/12/02	Adderall XR 20 mg	Adderall 20 mg	Actual Error. A prescription for Adderall XR 20 mg was dispensed with Adderall 20 mg. The pharmacist did not realize that an extended release form of Adderall was available. The patient experienced no adverse outcome.
8	3932307-6	3/25/02	Glucophage XR	Glucophage	Actual Error. Patient received wrong formulation of Glucophage with wrong directions after refilling of old prescription number when patient had seen physician who ordered the new drug but forgot to mention XR form.

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/s/

Denise Toyer
9/6/02 09:29:57 AM
PHARMACIST

Jerry Phillips
9/6/02 10:13:15 AM
DIRECTOR

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: ODS Request
HFD-400
Parklawn Bldg/Room 15B-03
Attention: Sammie Beam, Project Manager

FROM: Division of Neuropharmacological Drug Products
HFD-120
Woodmont II Bldg

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/11/02		21-434		4/1/02

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xanax XR			8/26/02

NAME OF FIRM: Pharmacia & Upjohn

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Please find attached the labeling for pending NDA 21-434. The sponsor has chosen to submit a second tradename for consideration. If you should have any questions, please call at: 594-5535 (I am covering for PM Melaine Shin).**

Thank You

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

(J)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:			FROM:	
HFD-009 Controlled Substance Staff Attn: Corinne Moody			HFD-120	
DATE 10-8-02	IND NO.	NDA NO. 21-434	TYPE OF DOCUMENT: **New NDA**	DATE OF DOCUMENT 1-9-02
NAME OF DRUG Xanax XR	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NAME OF FIRM: Pharmacia & Upjohn				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE--NDA MEETING	RESPONSE TO DEFICIENCY LETTER
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW
ADVERSE REACTION REPORT	PAPER NDA	CORRESPONDENCE
MANUFACTURING CHANGE/ADDITION	CONTROL SUPPLEMENT	FORMULATIVE REVIEW
MEETING PLANNED BY		OTHER *(SPECIFY BELOW)* :

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER (SPECIFY BELOW):	CHEMISTRY REVIEW PHARMACOLOGY BIOPHARMACEUTICS OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS (List below)	POISION RICK ANALYSIS
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:	
See attached.	
SIGNATURE OF REQUESTER Melaine Shin(4-5793) Shinm@cder.fda.gov	METHOD OF DELIVERY (Check one) MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Melaine Shin
10/8/02 10:46:21 AM

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MEMORANDUM OF TELEPHONE CONVERSATION

NDA#	21-434
DATE:	08-AUG-02
PRODUCT NAME:	Xanax XR
FIRM NAME:	Pharmacia & UpJohn
SUBJECT:	Response to Amendment dated 17-JUL-02
CONVERSATION WITH:	Ms.. Tammy Sanders
TELEPHONE No.:	(616) 833-9257

BACKGROUND: A response to sponsor question's in amendment dated 17-JUL-02

****

08-AUG-02: Spoke with Ms. Tammy Sanders.

Question 1: The sponsor was interested as to whether the proposed scheduled outlined in Amendment, dated 17-JUL-02, would provide sufficient time to conduct a review of the stability data.
FDA response: In this specific case, the answer is yes.

Question #2: What will the impact of submitting —— of 40°C/75%RH stability data have on the expiry?
FDA response: Expiry will be determined by the amount of stability data submitted and its quality (review issue).

Question #3: Is it reasonable to expect that with the data submitted, plus the supportive data, a —— expiry would be set?
FDA response: Expiry will be determined by the amount of stability data submitted and its quality (review issue).

/S/

Thomas F. Oliver, Ph.D.

cc: NDA 21-434
HFD-120/DivFile
HFD-120/TOliver
HFD-120/LRocca
HFD-120/PM/AMHomonnay

File: memo21-434.t01

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Thomas Oliver
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CHEMIST

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-434

Pharmacia & Upjohn
Attention: Roma Thomas
Regulatory Manager
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Thomas:

Please refer to the meeting between representatives of your firm and FDA on May 10, 2002. The purpose of the meeting was to discuss stability data issues concerning pending NDA 21-434.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you shouldhave any questions, please call Ms.Anna Marie H. Weikel, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

/S/

{See appended electronic signature page}

Hasmukh Patel, Ph.D.
Acting Chemistry Teamleader, Psychiatric Drugs
Division of Neuropharmacological Drug Products
Office of New Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

TELECONFERENCE MINUTES

DATE: May 10, 2002
NDA: 21-434
DRUG: Xanax XR® (alprazolam) Tablets
LOCATION: WOC II, Conference Room E
INDICATION: ———
PARTICIPANTS:

FDA Division of Neuropharmacological Drugs
Hasmukh Patel, Ph.D., Acting Chemistry Team Leader, Psychiatric Drugs
Lorenzo Rocca, Ph.D., Chemistry Reviewer
Ramana Uppoor, Ph.D., Biopharmaceutics Team Leader
Wendy Chou, Pharm D, Ph.D., Biopharmaceutics Reviewer

Pharmacia & Upjohn
Mark Ammann, Sr. Global Director CNS
Peter DiRoma, Associate Director Regulatory Affairs
Roma Thomas, Manager Regulatory Affairs
Beth Freeman, Sr. Research Scientist CMC Documentation
Paul Allen, Sr. Research Scientist CMC Documentation
Mark VanArendonk, Sr. Director Pharmaceutical Sciences Operations
Sharon Olmstead, Executive Director, US Regulatory Liaison.

BACKGROUND:
The sponsor requested this teleconference to seek FDA agreement on the amount and type of stability data that is proposed for this pending NDA in order to obtain a ——— expiration date for this product. In addition, they were seeking FDA agreement on the acceptability of adding a debossed marking on the tablet. A meeting package was submitted on April 26, 2002, with details about their proposals and the teleconference focused on the questions posed in this briefing package.

DISCUSSION:

Since ——— shelf life is important to ensure the commercial viability of Xanax XR® Tablets, Pharmacia & Upjohn is seeking FDA agreement that the existing stability and impurities data submitted in pending NDA 21-434 in conjunction with a ——— accelerated stability data update in the Fall would be adequate to grant a ——— expiry for the drug product.

FDA remarked that the stability data submitted in the NDA, European data under non-ICH conditions as well as other data, was not considered to be the primary stability data critical to determining the expiration date of the product per ICH guidelines. Nevertheless, it would be considered supportive stability data.

The sponsor said they will be prepared to submit time zero stability data from their facility in Puerto Rico by July 2002; however, the [redacted] stability data update would not be available until October 2002 which would closely coincide with the October 26, 2002, PDUFA action date of the application. The firm asked whether the review clock will be extended. FDA said that consideration will be given to extending the review clock but that this was unlikely. FDA concluded that they will consider all of the stability data in its totality in determining the expiration date when the [redacted] primary stability data has been submitted in October 2002.

The sponsor asked whether FDA has to have the primary stability data for this product. FDA said that we do need the primary stability data as the data submitted in the NDA are not for the market product in the proposed market container and there is no way to access the stability of the market product and its shelf-life. According to the sponsor, drug product formulation for the European stability data is similar to the proposed market product. In addition, the packaging configurations are slightly different.

The sponsor plans to add debossed markings to Xanax XR® Tablets and maintains that the additions of these markings is well within the range of variations that have already been studied. Does FDA agree?

The sponsor said that they plan to manufacture a validation batch of debossed tablets in [redacted] with the release data available by the end of that month. FDA said that the data submitted in the briefing document did not fully address the debossing issue since those only address changes in shape and not debossing on both sides of the tablet. In addition the Belgian formulation data is not very useful since there are several differences in the shape, debossing and color of these tablets and the US tablets.. Therefore a full comparative dissolution profile between the debossed and un-debossed tablets for each tablet strength, based on the F2 comparison, will be required using the selected dissolution method.

ACTION ITEMS:

1. The sponsor will submit the time zero stability data in [redacted] for FDA review.

2. The sponsor will submit the comparative dissolution data for the debossed tablets from the validation batch in [redacted] for FDA review.

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/s/

Hasmukh Patel
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 23,179

Pharmacia & Upjohn
Attention: Roma Thomas
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Thomas:

Please refer to the meeting between representatives of your firm and FDA on July 19, 2001. The purpose of the meeting was to reach agreement on the acceptability of the information that will be included in a proposed NDA for alprozolam XR tablets.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melaine Shin, R.Ph., Regulatory Management Officer, at 301-594-5793.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Application:	IND 23,179
Drug:	Xanax XR Tablets
Indication:	[redacted]
Sponsor:	Pharmacia & Upjohn
Meeting Type:	Pre-NDA Meeting
Date:	July 19, 2001 / 1:00PM
Place:	Woodmont II, Conference Room E

FDA Attendees:

Russell Katz, M.D.	Division Director
Thomas Laughren, M.D.	Clinical Team Leader
Paul Andreason, M.D.	Medical Officer
Ramana Uppoor, Ph.D.	OCPB Team Leader
Gerald Fetterly, Ph.D.	OCPB Reviewer
Kun Jin, Ph.D.	Biometrics Team Leader
Ohidul Siddiqui, Ph.D.	Biometrics Reviewer
Melaine Shin, R.Ph.	Regulatory Management Officer

Pharmacia & Upjohn Attendees:

Kerry Barker, Ph.D.	Sr. Biostatistical Scientist
Michael D. Burdick	Associate Director, Regulatory Affairs
Angel Canales	Sr. Director, Regulatory Affairs
Joseph C. Fleishaker, Ph.D.	Director, Clinical Pharmacology
Leonie W. Frank	CNS Project Management
Christopher C. Gallen, M.D.	VP CNS Medical Development
Francois Meurgey	Sr. Director CNS Products
Philip D. Perera, M.D.	CNS Medical Development
Roma J. Thomas	Manager, Regulatory Affairs
C. Eugene Wright, Ph.D.	CNS Project Leader

Background:

Pharmacia & Upjohn (P&U) requested this meeting to seek agreement with FDA on the acceptability of the information that will be included in a proposed NDA for alprazolam XR Tablets. In 1991, the Upjohn Company submitted an NDA for alprazolam XR based on bio data and one positive clinical study. Since the new formulation was not bioequivalent with the approved formulation, clinical studies were needed, and at the time, DNDP policy required two such studies. The sponsor subsequently [redacted]

Discussion:

- FDA stated that P&U would be required to conduct only a single efficacy study, along with pharmacokinetic characterization of alprazolam XR and its safety data, as a basis for approval.

However, FDA would be interested in Pharmacokinetic/Pharmacodynamic relationships including a full analysis of the results.

- FDA prefers to have a single label for both formulations.
- Based on the summary information provided, this application would likely be filable. However, this would be a matter for review at the time of actual filing.
- P&U would be [redacted]
- It was noted that the clinical efficacy trial was conducted with once a day dosing of alprazolam XR. In order to support bid dosing with the XR, they would need to show that plasma concentrations for bid dosing with the XR fall between those with qd dosing with the XR and qid dosing with the IR.
- A literature search and a synopsis of current ADME and drug-drug interaction data with alprazolam should be included in the submission.
- An *in vitro* assessment of the metabolism of alprazolam and potential drug interactions should be done if not found in literature.
- Development of an *in vitro - in vivo* correlation of the new formulation should be included in the submission if sufficient data are available.
- Electronic submission of all Clinical Pharmacology, Pharmacokinetic, and Clinical Trial studies is requested.
- It was noted that the to-be-marketed XR formulation should be identical to the formulation submitted in the 1991 NDA.

Post Meeting Note:

P&U will submit a briefing package for the CMC section of the application. If needed, a teleconference would be scheduled for a discussion with the Division's CMC review team.

Action Item:

- Prepare and circulate the Meeting Minutes.

/S/

Melaine Shin, R.Ph.
Meeting Recorder

/S/

Thomas Laughren, M.D.
Chair Concurrence

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Thomas Laughren
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Signed for Russell Katz, M.D.

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