

ANDA 19-908

Ambien

Pharm. Memos  
Exclusivity Summ.

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: November 19, 1991

FROM: Glenna G. Fitzgerald  
Acting Supervisory Pharmacologist  
HFD-120

SUBJECT: Recommendation by Dr. Wilk for repeat carcinogenicity  
study in rats

TO: NDA 19-908

The only toxicological issue which needs to be addressed for zolpidem is the occurrence in high dose rats of an increased incidence of renal liposarcomas (3/50 males and 1/50 females). No control rats developed this relatively rare tumor. There was also one benign lipoma in a male rat receiving middle dose. Historical control data supplied by the sponsor indicate that the finding of 3/50 tumors in male rats represent an occurrence which is slightly higher than the usual spontaneous rate for this tumor.

Because of its indication as a hypnotic, Dr. Wilk has requested that the sponsor perform a repeat carcinogenicity study as soon as possible, using special lipid stains for renal tissues in order to more accurately evaluate the relationship between zolpidem administration and the potential development of renal liposarcoma.

It is my recommendation at this time that the labeling reflect this tumorigenic response. Additional preclinical requirements should not be transmitted to the sponsor until the data have been reviewed by the CDER Carcinogenicity Assessment Committee prior to approval of zolpidem.

*NDA 19-908  
19-908 Div File*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

UM  
19-908

## Memorandum

Date April 17, 1992  
From Judi Weissinger, Ph.D., HFD-502  
Assistant Director (Pharmacology/Toxicology)  
Subject Ambien (zolpidem) Approvable Package  
To Merrill J. Mille, R.Ph.  
CSO, HFD-120

Please accept this written memorandum as confirmation of verbal communications regarding Zolpidem toxicity issues.

### Carcinogenicity:

There appears to be no need to convene a Carcinogenicity Assessment Committee at this time to consider the results of the two year dietary carcinogenicity study in the rat.

Renal liposarcoma and lipoma combined were 0, 0, 2, 6% for males and 0, 0, 0, 2% for females. The historical incidence, for studies conducted within four years of this zolpidem study is 0-4%. Additionally, thyroid follicular adenoma and carcinoma combined was 6, 8, 10, 12% for males, and 6, 4, 8, 10% for females with no change in TSH reported. Testicular interstitial cell adenoma were 6, 8, 10, and 12%. The statistical significance was limited to the renal findings.

Information relating to lipomas should be included in the labeling, with comment only on the lack of knowledge of the effect in humans. It is generally inappropriate to specify a lack of relationship where information on the mechanism of the effect is not available.

The utility of repeating the carcinogenicity study should be considered prior to supporting the suggestion of the review. A repeat study that is negative will not erase this study. A repeat study that confirms similar weak findings (in the presence of similar weight loss in the high dose groups) would not offer additional information on which to base a prediction of human safety.

Humans have a rapid absorption and rapid elimination; neither high dose point insults to tissue nor accumulation of drug is expected to occur. The results of a single dose of 15 mg, 1/30 the lowest renal lesion dose over a lifetime in rats (based on a mg/m<sup>2</sup> comparison), suggests that we do not have a level of concern that would be altered by repeating the two year study.

Change in synthesis:

As was orally confirmed with Dr. Contrera, a change in synthesis is acceptable with appropriate bridging studies. This is a general policy, and the bridging studies usually suggested are the 3 month toxicity and the reproductive segment II studies. Appropriate studies are alternatively determined based on the existing data on the specific compound. The repeat dose and genotoxicity studies conducted are acceptable bridging studies. No increase in toxicity at comparable doses was observed when compared to the original lots. This is acceptable confirmation that additional toxicity is not associated with impurities resulting from the new synthesis. A record of the impurity profile with the original synthesis and the new synthesis should be retained.

ORIG  
Package

EXCLUSIVITY SUMMARY FOR NDA # 19-908

SUPPL # \_\_\_\_\_

Trade Name ~~STRENGTH~~ Ambien

Generic Name Zolpidem tartrate

Applicant Name LOREX

HFD # 120

Approval Date If Known \_\_\_\_\_

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type? (SE1, SE3, etc.) \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:  
\_\_\_\_\_  
\_\_\_\_\_

Revised 5-90

cc: Original NDA

Division File

HFD-84

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength and route of administration, previously been approved by FDA for the same use?

YES /\_\_\_/ NO /X/

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

#### PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

##### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ /      NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

\_\_\_\_\_  
\_\_\_\_\_

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_\_\_/



(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:  
\_\_\_\_\_  
\_\_\_\_\_

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

\_\_\_\_\_  
\_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!	
IND # _____	YES /___/	!	NO /___/ Explain: _____
		!	_____
Investigation #2		!	
IND # _____	YES /___/	!	NO /___/ Explain: _____
		!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		!	
YES /___/ Explain _____		!	NO /___/ Explain _____
_____		!	_____
_____		!	_____
Investigation #2		!	
YES /___/ Explain _____		!	NO /___/ Explain _____
_____		!	_____
_____		!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /  /      NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

Manil J. Mello  
Signature  
Title: CSO

1/31/91  
Date

[Signature]  
Signature of  
Division Director

1/31/91  
Date

# EXCLUSIVITY DETERMINATION CHECKLIST

A # \_\_\_\_\_ SUPPL. # \_\_\_\_\_ APPLICANT \_\_\_\_\_ TR. NAME \_\_\_\_\_

ACTIVE INGRED. \_\_\_\_\_ POTENCY \_\_\_\_\_ DOSAGE FORM/ROUTE \_\_\_\_\_

APPROVAL DATE \_\_\_\_\_

TYPE OF APPLICATION: FULL NDA \_\_\_\_\_ 505(b)(2) \_\_\_\_\_ EFFIC. SUPP. \_\_\_\_\_ OTHER (SPECIFY) \_\_\_\_\_

EXCLUSIVITY REQUESTED: 5 YR \_\_\_\_\_ 3 YR \_\_\_\_\_ NONE \_\_\_\_\_

**QUALIFICATIONS FOR 5 YR EXCLUSIVITY:**

Approved for NCE, no salt or ester of which previously approved

**QUALIFICATIONS FOR 3 YR EXCLUSIVITY:**

Approval based on clinical study (other than BIO)?	Y _____	N _____	
<b>New Studies:</b>			
Previously relied on by Agency for efficacy?		Y _____	N _____
<b>Essential for Approval:</b>			
Approval could have been based on literature?		Y _____	N _____
Previously approved in another application?		Y _____	N _____
<b>Studies conducted by or for applicant:</b>			
IND sponsored by applicant?	Y _____	N _____	
or Certification of principal support?	Y _____	N _____	

NOTE: If any checks appear in shaded area, it is likely that exclusivity should not be granted. Any exclus. recommendations should be explained below:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

EXCLUSIVITY RECOMMENDED: 5 YR \_\_\_\_\_ 3 YR \_\_\_\_\_ NONE \_\_\_\_\_

CONCUR \_\_\_\_\_  
NON CONCUR \_\_\_\_\_ )

SIGNED \_\_\_\_\_  
DIRECTOR, OFFICE OF GENERIC DRUGS