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RESEARCH**

**APPLICATION NUMBER: 17-892/S-034**

**CLINICAL PHARMACOLOGY  
BIOPHARMACEUTICS REVIEW**

**Supplemental New Drug Application  
Clinical Pharmacology and Biopharmaceutics Review**

<b>NDA:</b>	17-892 SLR-034
<b>Type of Submission:</b>	Supplement – Labeling
<b>Generic Name:</b>	Triazolam
<b>Brand Name:</b>	Halcion® Tablets
<b>Formulation(s); Strength(s); Route(s)</b>	Tablets — Immediate-Release 0.125 mg. 0.25 mg PO
<b>Sponsor:</b>	Pharmacia and UpJohn Kalamazoo, Michigan
<b>Submission Date:</b>	August 20, 1998
<b>Consult Request Date:</b>	September 04, 2002
<b>Reviewer:</b>	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
<b>Team Leader</b>	Raman Baweja, Ph.D.
<b>OCPB Division</b>	Division of Pharmaceutical Evaluation 1 (DPE1) HFD-860
<b>ORM Division</b>	Division of Neuro-psychiatric Drug Products (DNPDP) HFD-120
<b>Indication:</b>	Insomnia
<b>Therapeutic Class:</b>	Hypnotic

## 1 EXECUTIVE SUMMARY

The present submission is in response to the August 27, 1997 Federal Register notice of priority implementation of geriatric use statements for hypnotic drugs.

The sponsor proposes addition of labeling to the end of the Clinical Pharmacology section and a Geriatric Use Statement at the end of the Precautions section. No other labeling changes are proposed.

The essence of the proposed statements is that the elderly are more susceptible to dose related adverse effects, specifically sedation, psychomotor coordination and other effects, and that this increased susceptibility is due to higher concentrations \_\_\_\_\_

\_\_\_\_\_ An article published in the New England Journal of Medicine (NEJM) was submitted to support the proposed labeling. However, the claimed \_\_\_\_\_

\_\_\_\_\_ not well supported by this article. For the higher concentrations mechanisms other than \_\_\_\_\_ are more consistent with the data. In addition, the claimed \_\_\_\_\_ does not appear to hold up upon critical analysis.

The NEJM article does provide additional support for the current labeling with regards to increased susceptibility to adverse effects and the recommended use of lower dosages in the elderly in the Warnings, Precautions and Dosage and Administration sections. That is, use in the elderly of half the dosage used in younger patients as currently labeled. Consequently, no further changes are requested to these sections of the current labeling by the sponsor.

### 1.1 OCPB RECOMMENDATIONS

The sponsor's proposed changes are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics with modification.

Labeling comments should be communicated to the sponsor as appropriate (see Section 1.2 Labeling Comments on page 2).

**1.2 LABELING COMMENTS**

SPONSOR'S PROPOSAL	OCPB PROPOSAL
<p><b>CLINICAL PHARMACOLOGY</b></p>	<p><b>CLINICAL PHARMACOLOGY</b></p> <p>... In a study of elderly (62 - 83 years old), versus younger subjects (21 - 41 years old), who received HALCION at the same dose levels, (0.125 mg and 0.25 mg), the elderly experienced both greater sedation and impairment of psychomotor performance. These effects resulted largely in higher plasma concentrations of triazolam in the elder</p>
<p><b>WARNINGS</b></p> <p>... Because some of the adverse effects of HALCION appear to be dose related (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), it is important to use the smallest possible effective dose. Elderly patients are especially susceptible to the dose related adverse effects.</p>	<p>(Sponsor's Proposal is Acceptable.)</p>
<p><b>PRECAUTIONS</b></p> <p>... <b>Geriatric Use:</b> The elderly are especially susceptible to the dose related adverse effects of HALCION. They exhibit higher plasma triazolam concentrations due to reduced clearance of the drug as compared with younger subjects at the same dose. To minimize the possibility of development of oversedation, the smallest effective dose should be used (see CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION.)</p>	<p>(Sponsor's Proposal is Acceptable.)</p>
<p><b>DOSAGE AND ADMINISTRATION</b></p> <p>... The recommended dose for most adults is 0.25 mg before retiring.... In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.</p>	<p><b>DOSAGE AND ADMINISTRATION</b></p> <p>... The recommended dose for most adults is 0.25 mg before retiring.... In geriatric and/or debilitated patients the recommended dosage range is 0.125 mg to 0.25 mg. Therapy should be initiated at 0.125 mg in these groups and the 0.25 mg dose should be used only for exceptional patients who do not respond to a trial of the lower dose. A dose of 0.25 mg should not be exceeded in these patients.</p>

## 2 REVIEW

The sponsor submitted the following article in support of the proposed labeling:

Greenblatt DJ, Harmatz JS, Shapiro L, Engelhardt N, Gouthro TA, Shader RI. Sensitivity to Triazolam in the Elderly. N Engl J Med. June 13 1991; 324: (24) 1691-8.

### Study Design

This was a blinded placebo controlled 4-way crossover study in 26, (15/11 M/F), healthy young adults 21 – 41 years old and in 21, (5/16 M/F), elderly subjects 62 – 83 years old. There was a minimum of a 1 week inter-period washout between treatments.

In the first arm each subject took a single AM dose of placebo in a single blind fashion, the 3 subsequent arms were double-blinded and subjects took a single AM dose of placebo or triazolam 0.125 mg or 0.25 mg 2 – 3 hours after a 'light breakfast' of orange juice.

Table 1 Assessments

Test		Baseline	Postdose Sampling Time (hours)									
			0.5	1	1.5	2	2.5	3	4	6	8	24
PK <sup>1</sup>	Triazolam	X	X	X	X	X	X	X	X	X	X	X
	BZPs <sup>3</sup>	X										
PD <sup>2</sup>	Sedation - Self Assessment by 100 mm VAS <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X
	Sedation - Observer Rated by 100 mm VAS	X	X	X	X	X	X	X	X	X	X	X
	Mood - Self Assessment by 100 mm VAS	X	X	X	X	X	X	X	X	X	X	X
	Mood - Observer Rated by 100 mm VAS	X	X	X	X	X	X	X	X	X	X	X
	DSST <sup>5</sup>	X	X	X		X		X	X	X	X	X
	Immediate Word Recall	X			X							X
	Delayed Word Recall	X										X

1 PK – pharmacokinetic of heparinized plasma by gas chromatography, 2 PD – Pharmacodynamic, 3 BZP – benzodiazepines, 4 VAS – visual analog scale, 5 DSST – digital symbol substitution test

### Results and Comments

Plasma concentrations were dose proportional with concentrations in the elderly higher than in young adults at both doses.

The article and sponsor both attributed this to a decrease in clearance in the elderly (~40% – 45%), however although C<sub>max</sub> was increased, neither T<sub>max</sub> nor half-life was altered. The lack of change in half-life with such a large change in Cl/F is inconsistent. There does not seem to be a weight change that would compensate for this by a decrease in volume of distribution, although the article does claim that the difference in gender between groups was examined and was not an important covariate. However, a difference in habitus or other gender effect can't be ruled out as raw data is not available to examine.

It's possible that the observed increase in concentrations is due to an increase in bioavailability (F). Triazolam is acid labile and bioavailability has been shown to increase on the order of 30% in the

presence of acid suppressants. Standard texts (e.g. Merck Manual of Geriatrics) indicate that gastric pH is much higher in the elderly and this may largely explain the increase in exposures.

Ranking of mean relative exposures as follows:

young 0.125 mg < elderly 0.125 mg < young 0.25 mg < elderly 0.25 mg.

Mood was not reported.

Sedation as ranked by self assessment was as follows:

Young: placebo < 0.125 < 0.25 mg

Elderly: Placebo < 0.125 mg  $\cong$  0.25 mg

Sedation as ranked by blinded observers was the same rank order as drug exposure for the time points up to ~2 hours. However, from 2 – 8 hours the elderly had greater mean sedation than the young subjects even when concentrations were lower in the elderly. This suggests either a pharmacodynamic difference or altered pharmacokinetics of an active metabolite. There are active metabolites, although based upon a cursory inspection of the literature there is insufficient information to determine the likelihood of this hypothesis.

Similar results were observed with the DSST.

A linear function was fit to mean PK/PD data (DSST) and no statistical difference in the slopes of the fit for the different age groups were found. However, there is a trend for separation at the lower concentrations as expected based upon the above description. Consequently, a difference might simply not have been detected due to lack of using an Emax function and due to the weighting of the fits by the greater amount of data from the earlier time points.

Both immediate and delayed word recall were effected by triazolam in a dose dependent manner in both groups with no residual effects. The elderly had a worse baseline ability for immediate word recall, (i.e. under placebo conditions), and this appears to be the major cause for all differences observed. Consequently, although an amnestic effect was observed there does not appear to be any major differences of triazolam on memory between the elderly and the young.

### 3 SIGNATURES

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Ronald E. Kavanagh, BS Pharm, Pharm.D., Ph.D., OCPB/DPE-1

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Date

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Raman Baweja, Ph.D., Team Leader, OCPB/DPE-1

\_\_\_\_\_  
Date

CC:

NDA 17-892 (orig., 1 copy)  
HFD-120 (DavidP, AndreasonP, LaughrenT, KatzR)  
HFD-860 (Baweja, KavanaghR, Mehta))  
CDR (B.Murphy)

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/s/

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10/2/02 02:38:00 PM  
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10/2/02 05:06:40 PM  
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