

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 17-892/S-034

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 17-892
Sponsor: Pharmacia & Upjohn
Drug: Halcion ®, triazolam
Indication: hypnotic
Dates of Submission: August 20, 1998
Materials Reviewed: S-034 Geriatric labeling supplement

Background

Triazolam is a short-acting benzodiazepine hypnotic agent. The sponsor proposes draft labeling for a _____ sub-section. Language in this draft labeling is supported by an attached article Greenblatt DJ et al., "Sensitivity to triazolam in the elderly", *NEJM* 324:24; 1691-1698, 1991.

The article summarizes a pharmacokinetic and pharmacodynamic study of two doses (0.125 and 0.25-mg) of triazolam in elderly and young adult subjects. The study analyzed the standard PK parameters including C_{max}, AUC, T_{max}, clearance, and t_{1/2}. Pharmacodynamic parameters included subject reported sedation on a 10-cm VAS and DSST. Increases in C_{max} and AUC were proportional between the dose groups but C_{max} and AUC were respectively 50% and 70% higher in the elderly versus young adults. Clearance in the elderly was half that of the young adults. Performance differences on drug versus baseline for the DSST was significantly worse in the elderly at 4 hours (p<0.05) and 8-hours (p<0.001) after dosing.

The proposed language states:

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.

These labeling changes are acceptable from a clinical standpoint.

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