CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-227 / S-012

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 18-227, SLR-12	**Submission Date**: August 28, 1998
Name: Amidate® (Etomidate injection)	
Sponsor: Abbott Laboratories, 200 Abbott Park Rd. Abbott Park, IL 60064-3537	
Type of Submission: Labeling supplement	**Reviewer:** Shinja R. Kim, Ph.D.

Background

Amidate® is a hypnotic drug without analgesic activity indicated for the induction of general anesthesia, at doses ranging from 0.2 to 0.6 mg/kg of body weight.

The sponsor submitted a supplemental application per 201.57 CFR (f)(10); "Specific requirement on content and format of labeling for human prescription drugs", addition of 'Geriatric Use' subsection. This submission contained articles providing information relating to the use of this drug in elderly patients to support the revision of the package insert for Amidate®. Revised labeling statements in Package Inserts per sponsor are shown in Attachment.

Summary of the articles submitted in the package

(1) Carlos et al. 1981 reported that elderly subjects (seventeen healthy, aged 70 to 90 years) showed a higher percentage (43.6 ± 2.8%) of unbound etomidate compared to that (24.9 ± 1.4%) of younger subjects (ten healthy, aged 20 to 35 years).

(2) Pharmacodynamic (53.5 ± 17.7 years) and the pharmacokinetic (56.7 ± 18 years) study was carried out by Arden et al. 1986. The results of this study are as follows:

Pharmacodynamic analysis; The mean dose of etomidate required to reach stage-III anesthesia significantly decreased with increasing age (0.134 mg/kg in an 80-year-old patient *vs* 0.725 mg/kg in a 22-year-old patient). However, the slope of the concentration versus effect curve and the rate of equilibrium between the blood and site of action in the brain ($T_{1/2}$, keo) did not change with increasing age.

Pharmacokinetic analysis; Initial distribution volume decreased with increasing age ($r = 0.56$) , however, there was no significant change in mean steady-state volume of distribution. Total clearance decreased with age, declining approximately 2ml/kg/min for every decade in the age range studied.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics reviewed this submission. The revised labeling regarding 'Geriatric Use' in the package insert is acceptable.

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Division of Pharmaceutical Evaluation II

RD/FT_____ Ramana Uppoor, Ph.D., Team Leader

cc: NDA (18-227), HFD-170 (Divisional File, Medical Officer, Morgan), HFD-870 (ChenME, Uppoor, Kimsh), HFD-850 (Lesko), CDR (Barbara Murphy)

WITHHOLD 8 PAGE(S)

Draft labeling

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