CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-157 / S-018

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Generic Name:	Prednisolone Sodium Phosphate, USP Oral Solution
Sponsor:	Celltech Pharmaceuticals, Inc., Rochester, NY
NDA:	19-157 (SLR-018)
Submission Date:	8/21/03
Brand Name:	Pediapred®
Reviewer:	Tapash K. Ghosh

Review of Geriatric Labeling Supplement Request

Pursuant to the regulations at 21CFR201.57(f)(10), the sponsor has requested addition of new text in the "Clinical Pharmacology" and "Geriatric Use" subsections of their approved label for Pediapred®. The sponsor did not conduct any clinical study targeted for geriatric population. However they cited the following published article to craft their language:

"Stuck, AE, Frey, BM, Frey FJ. Kinetics of prednisolone and endogenous cortisol suppression in the elderly. *Clin. Pharmacol Ther.,* 1988, 43:354-62."

Recommendation:

The sponsor's request in alternative wording in adding the proposed statement into the Pediapred® labeling regarding use in the geriatric population is acceptable from a biopharmaceutics perspective with the suggested modifications:

CLINICAL PHARMACOLOGY:

The systemic availability, metabolism and elimination of prednisolone after administration of single weight-based doses (0.8 mg/kg) of intravenous (IV) prednisolone and oral prednisone were ~~investigated~~ reported in a small study of 19 young (23 to 34 years) and 12 elderly (65 to 89 years) subjects. Results showed that the systemic availability of total and unbound prednisolone, as well as interconversion between prednisolone and prednisone were independent of age. The mean unbound fraction of prednisolone was higher, and the steady-state volume of distribution (Vss) of unbound prednisolone was reduced in elderly patients. Plasma prednisolone concentrations were higher in elderly subjects, and the higher AUCs of total and unbound prednisolone were most likely reflective of an impaired metabolic clearance, evidenced by reduced fractional urinary clearance of 6β-hydroxyprednisolone. Despite these findings of higher total and unbound prednisolone concentrations, elderly subjects had higher AUCs of cortisol, suggesting that the elderly population is less sensitive to suppression of endogenous cortisol or their capacity for hepatic inactivation of cortisol is diminished. ~~Thus, although pharmacokinetic analyses may indicate that reduced doses of prednisolone might be appropriate in elderly patients, these pharmacokinetic differences might be counterbalanced by a reduced biologic efficacy (e.g., reduced responsiveness of target organs) of prednisolone in this population, as evidenced by decreased suppression of endogenous cortisol concentrations in the elderly.~~

Geriatric Use: Clinical studies of PEDIAPRED did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience with prednisolone sodium phosphate has not identified differences in

responses between the elderly and younger patients. However, the incidence of corticosteroid-induced side effects may be increased in geriatric patients and appear to be dose-related. Osteoporosis is the most frequently encountered complication, which occurs at a higher incidence rate in corticosteroid-treated geriatric patients as compared to younger populations and in age-matched controls. Losses of bone mineral density appear to be greatest early on in the course of treatment and may recover over time after steroid withdrawal or use of lower doses (i.e., ≤5 mg/day). Prednisolone doses of 7.5 mg/day or higher have been associated with an increased relative risk of both vertebral and nonvertebral fractures, even in the presence of higher bone density compared to patients with involutional osteoporosis.

Routine screening of geriatric patients, including regular assessments of bone mineral density and institution of fracture prevention strategies, along with regular review of prednisolone indication should be undertaken to minimize complications and keep the prednisolone dose at the lowest acceptable level. Co-administration of bisphosphonates has been shown to retard the rate of bone loss in corticosteroid-treated males and postmenopausal females, and these agents are recommended in the prevention and treatment of corticosteroid-induced osteoporosis.

It has been reported that eEquivalent weight-based doses yield higher total and unbound prednisolone plasma concentrations and reduced renal and non-renal clearance in elderly patients compared to younger populations. However, it is not clear whether dosing reductions would be necessary in elderly patients, since these pharmacokinetic alterations may be offset by age-related differences in responsiveness of target organs and/or less pronounced suppression of adrenal release of cortisol. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY).

Tapash K. Ghosh, Ph.D.
Pharmacokineticist
DPE III

Team Leader: E. Dennis Bashaw, Pharm.D. _____

CC: NDA 19-157 (Orig)
HFD-550/Div File
HFD-540/CSO/Gould
HFD-880(Bashaw/Ghosh)
HFD-880 (Lazor/Selen)

Attachment: Sponsor's proposed label

WITHHOLD 11 PAGE(S)

Draft Labeling

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

/s/

Tapash Ghosh
2/25/04 06:12:10 PM
BIOPHARMACEUTICS

Dennis Bashaw
2/26/04 05:13:00 PM
BIOPHARMACEUTICS