CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-803

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-803	**SUBMISSION DATE:** 1/31/97
PRODUCT: Loteprednol Etabonate, 0.2% Ophthalmic Suspension	
SPONSOR: Pharmos Corporation 2 Innovation Drive Alachua, Fl, 32615	**REVIEWER:** Dan Wang, Ph.D.
	TYPE OF SUBMISSION: Original

BACKGROUND

The applicant submitted NDA 20-803 for loteprednol etabonate ophthalmic suspension, 0.2%, for the treatment of the signs and symptoms of seasonal allergic conjunctivitis. Loteprednol etabonate (LE) is a corticosteroid with anti-inflammatory activity. It is a chemically unique derivative of prednisolone, the active form of prednisone. Its actions are of the glucocorticoid type with no detectable mineralocorticoid actions. LE was designed to address some of the side effects associated with other corticosteroids, such as increased intraocular pressure, increased incidence of posterior subcapsular cataracts after prolonged use, and increased susceptibility to infections of the eye.

NDA 20-803 is the second application from the applicant for loteprednol etabonate. NDA 20-583 was submitted on March 29, 1995 for loteprednol etabonate ophthalmic suspension, 0.5%. This NDA is not approvable because of clinical and chemistry deficiencies. The Human Pharmacokinetics and Bioavailability Section contained two pharmacokinetic studies and was reviewed by Dr. Ene Ette (Nov. 14, 1995). LE was studied after both topical ocular and oral administration. It was learned that orally administered LE was well absorbed and underwent extensive metabolism. Low levels of LE were detected in the systemic circulation, and it was converted to its metabolite, Δ^1cortienic acid etabonate, PJ-91. Analysis of plasma samples from a multiple dose ocular administration study (a 42 day study) showed that levels of LE and PJ-1 were below quantifiable limits Systemic absorption of LE via the ocular route is not extensive and there is no evidence of accumulation. Plasma cortisol levels were all within normal range, which indicated lack of adrenal suppression.

In this submission, the human pharmacokinetics and bioavailability section of NDA 20-583 has been referenced in support of NDA 20-803. Examination of 0.2% and 0.5% LE ophthalmic suspensions shows that these two formulations are very close (see attachment). As systemic exposure of loteprednol was minimal and there was no evidence of adrenal suppression following ocular administration of 0.5% LE ophthalmic suspension, it is not expected that the lower strength 0.2% LE ophthalmic suspension proposed in this application would produce significant systemic levels.

RECOMMENDATION

In the human pharmacokinetics and bioavailability section of NDA 20-803, reference is made to human pharmacokinetics and bioavailability information in NDA 20-583 (loteprednol etabonate ophthalmic suspension, 0.5%) which is of higher strength than that in the current NDA. The pharmacokinetic studies submitted in NDA 20-583 have been reviewed by Dr. Ene Ette and found acceptable. The pharmacokinetic study results of NDA 20-583 indicates there is limited systemic absorption of loteprednol etabonate with no evidence of adrenal suppression. Therefore, no additional pharmacokinetic study is needed for NDA 20-803 if the safety of this product is indicated in clinical trials. Please refer to NDA 20-583 Biopharm review for pharmacokinetics information of loteprednol etabonate.

LABELING COMMENTS

1. The following sentences need to be added before the first sentence of **Clinical Pharmacology** section: "The following pharmacokinetic information was obtained from a study of higher strength loteprednol etabonate ophthalmic suspension, 0.5%. No pharmacokinetic study has been conducted for 0.2% loteprednol etabonate ophthalmic suspension."

2. The last sentence of the first paragraph of **Clinical Pharmacology** section should be changed to "This study suggests that no minimal, if any, systemic absorption occurs with [TRADE NAME] Ophthalmic Suspension."

3/19/97

Dan Wang
Division of Pharmaceutical Evaluation III

FT initialed by D. Bashaw, Pharm.D. 3/20/97

cc:
NDA 20-803 (Original)
HFD-550(Holmes)
HFD-880(N. Fleischer)
HFD-880(Bashaw)
HFD-880(Wang)
HFD-344(Viswanathan)
CDR, Attn: Barbara Murphy

FORMULATIONS

Component	A[a] (mg)	B[b] (mg)
Loteprednol Etabonate,		
Glycerin, USP,		
Povidone, USP,		
Tyloxapol, USP		
Benzalkonium Chloride Solution.		
Edetate Disodium Dihydrate, USP		
Purified Water, USP	qs to 1.0 mL	qs to 1.0 mL
Hydrocholric Acid,	adjust pH	adjust pH
Sodium Hydroxide,	adjust pH	adjust pH

[a]Loteprednol etabonate 0.2% Ophthalmic solution
[b]Loteprednol etabonate 0.5% Ophthalmic solution