

## CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

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NDA 20-841

SUBMISSION DATE: 3/7/97

PRODUCT: Loteprednol Etabonate, 0.5%  
Ophthalmic Suspension

SPONSOR: Pharmos Corporation  
2 Innovation Drive  
Alachua, Fl, 32615

REVIEWER: Dan Wang, Ph.D.

TYPE OF SUBMISSION: Original

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### BACKGROUND

The applicant submitted NDA 20-841 for loteprednol etabonate ophthalmic suspension, 0.5%, for the treatment of post-operative inflammation following ocular surgery. The same product was submitted on March 29, 1995 under NDA 20-583 for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye, including anterior uveitis. This NDA is not approvable because of clinical and chemistry deficiencies. The applicant indicated that NDA 20-583 is currently under review by the Agency.

The data to support the new indication under NDA 20-841 were submitted in an amendment to NDA 20-583. No additional pharmacokinetic information was submitted in this NDA submission. The Human Pharmacokinetics and Bioavailability Section of NDA 20-583 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,  $\Delta^1$ cortienic 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/ [redacted] 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.

### RECOMMENDATION

As the product submitted under this NDA is the same product under NDA 20-583 and includes by right of reference the pharmacokinetic data that were previously submitted under NDA 20-583, no new studies are required. 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. Please refer to NDA 20-583 Biopharm review for pharmacokinetics information of loteprednol etabonate.