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REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 20-841

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ORIGINAL SUMMARY

SUBMISSION DATE: March 7, 1997
CENTER RECEIPT DATE: March 10, 1997
REVIEWER RECEIPT DATE: March 20, 1997
DRAFT REVIEW COMPLETE: April 21, 1997

SPONSOR: Bausch & Lomb, Pharmaceutical Division, 8500 River Parkway, Tampa, FL 33637.

DRUG: Loteprednol etabonate, 0.5%

PROPOSED INDICATION: Treatment of post-operative inflammation following ocular surgery.

RELATED DRUGS/INDs/NDAs: NDA 20-583 (0.5% loteprednol etabonate for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye, including uveitis); and NDA 20-803 (0.2% loteprednol etabonate for the treatment of the signs and symptoms of seasonal allergic conjunctivitis).

SUMMARY/REVIEW OF NONCLINICAL STUDIES: The nonclinical studies supporting this NDA are identical to the studies submitted to support NDA 20-583. The nonclinical studies for NDA 20-583 were reviewed by Dr. David A. Shriver of HFD-540. Dr. Shriver recommended approval for NDA 20-583. Dr. Shriver's review will be used to support NDA 20-841. A copy of the summary of Dr. Shriver's review is attached; the full review is archived with NDA 20-583. I reviewed the studies that are listed below to ensure that I agreed with Dr. Shriver's conclusions. I am in agreement with Dr. Shriver's conclusions.

Studies Submitted to NDA 20-583

Study Title	Volume:page
26-Week Ocular Dose Study in the Rabbit	9:1
52-Week Ocular Dose Study in the Dog	8:1
P-5604 Rat Teratology Study	13:1
P-5604 Peri and Post Natal Study	14:1
Fertility and General Reproductive	13:155
Loteprednol-Etabonate Rabbit Teratology Study	12:208
Mutagenicity Study of OPC-5604 by the Ames Test and in E.coli.	14:153

Study Title	Volume:page
Metaphase Analysis of Human Lymphocytes Treated with P-5604	14:132
Mouse Lymphoma L5178Y	14:210
Mouse Micronucleus Test	14:178

During my review of the genotoxicity studies, I noted deficiencies in the Ames and mouse lymphoma L5178Y tests. The Ames assay was conducted one time, and the results were negative. Negative results should be verified by a repeat assay; however, the sponsor did not repeat the Ames assay. In the case of the mouse lymphoma assay, negative results were obtained for the first assay. Although the sponsor repeated this assay to confirm the negative results, the second assay was unacceptable due to an inadequate response in the positive controls. Although the Ames and mouse lymphoma assays are deficient, the fact that negative results were obtained in both lends additional support to the sponsor's claim that loteprednol etabonate is nongenotoxic.

RECOMMENDATION: *The recommendation for this NDA is approval.*

RECOMMENDATIONS FOR LABELLING: These recommendations for labelling apply to NDA 20-583 also.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, three *in vitro* tests. *In vivo* evidence of genotoxicty, an increased frequency of micronucleated immature erythrocytes, was not observed in mice that received a single 4 gm/kg dose of loteprednol etabonate (8000 times the maximum daily clinical dose based on mg/m^2) Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (200 and 100 times the maximum clinical dose, respectively, based on mg/m^2) prior to and during mating did not impair fertility in either gender.

Pregnancy: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of menigiocele, abnormal left common carotjd artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day/day (24 times the maximum daily clinical dose based on mg/m^2), a dose which caused no maternal toxicity; the no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (4 times the maximum daily clinical dose based on mg/m^2). Oral treatment of rats during organogenesis with 50 or 100 mg/kg/day (200 and 400 times the maximum clinical dose, respectively, based on mg/m^2) resulted in embyotoxicity (increased post-implantation losses with 100 mg/kg/day, and decreased fetal body weight and skeletal ossification with 50 and 100 mg/kg/day); doses of 5 (20 times the maximum daily clinical dose based on mg/m^2), 50 and 100 mg/kg/day caused teratogenicity (absent inominate artery at all doses, and cleft palate and umbilical hernia at 50 and 100 mg/kg/day). Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to preganant rats during organogenesis at doses of 5 to 100 mg/kg/day but not at

0.5 mg/kg/day. The NOELs for the embryotoxic and teratogenic effects in rats were 5 mg/kg/day and 0.5 mg/kg/day (2 times the maximum daily clinical dose based on mg/m^2) for embryotoxicity and teratogenicity, respectively.

Oral exposure of pregnant rats to 5 and 50 mg/kg/day of loteprednol etabonate during the fetal period, a maternally toxic treatment regimen (significantly decreased body weight gain), resulted in teratogenicity (umbilical herniation) and embryotoxicity (decreased fetal birth weight); the NOEL for these effects was 0.5 mg/kg/day. Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5.0 mg/kg/day. Lotprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg day during the fetal period.

Oral treatment of female rats with 25 mg/kg/day (100 times the maximum daily clinical dosebased on mg/m^2) from prior to mating through parturition increased the duration of gestation.

[Reviewer's Comment: *The maximum clinical daily dose and the dose multiples were calculated as shown below:*

Clinical dose

0.5% = 0.5 gm/100 mL = 0.005 mg/uL
Assuming a 50 uL drop will be instilled into each eye 4 times daily the following calculation was made; 0.005 mg/uL x 50 uL/drop x 8 drops/day = 2.0 mg/day
Assuming a body weight of 50 kg, the dose will be 2.0 mg/day/50 kg = 0.04 mg/kg/day

Dose multiples

The calculation for the dose multiples are presented in the table below. The animal doses are those that were used in the labelling; the human dose is the maximum daily clinical dose.

Dose Multiples for NDA 20-841

Species	Dose in mg/kg/day	km	Dose in mg/m^2 (mg/kg x km)	Dose multiples (Nonclinical dose/clinical dose)
Mouse	4000	3	12,000	8000
Rabbit	3	12	36	24
	0.5		6	4
Rat	0.5	6	3	2
	5		30	20
	25		150	100
	50		300	200
	100		600	400
Human	0.04	37	1.50	---

20-841

/S/ 4-21-97

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cc:
Original NDA 20-841
Original NDA 20-583
HFD-550/Division Files
HFD-550/PM/Gunter
HFD-550/PM/Holmes
HFD-550/MO/Chambers
HFD-550/Pharm TL/Chen
HFD-550/Pharm/Weir

/S/ 4-25-97