CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-737

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880)** **Tracking/Action Sheet for Formal/Informal Consults**

From: **E.Dennis Bashaw, Pharm.D.**			**To: DOCUMENT ROOM (LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 12/20/04	IND No.: Serial No.:	NDA No. **21-737**	DATE OF DOCUMENT **ORIG-10/8/04** **120 Day Update-2/7/05**	
NAME OF DRUG **RETISERT (Fluocinolone Acetonide Intravitreal Implant) 0.59mg**	PRIORITY CONSIDERATION **1-P**		Date of informal/Formal Consult:	

NAME OF THE SPONSOR: [Bausch & Lomb, Inc.]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	XX OTHER *(SPECIFY BELOW)*: [ORIGINAL NDA]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	XX Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ • See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ • See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes dated:	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	[ ]	[]

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Recommendation

The sponsor has successfully demonstrated both the lack of systemic exposure and the relative degree of ocular release over time for this product. Based on the information provided by the sponsor, and our review of it, the sponsor has met the requirements of 21CFR 320 for this product. Labeling comments are also provided (pg. 7.)

Background

6 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

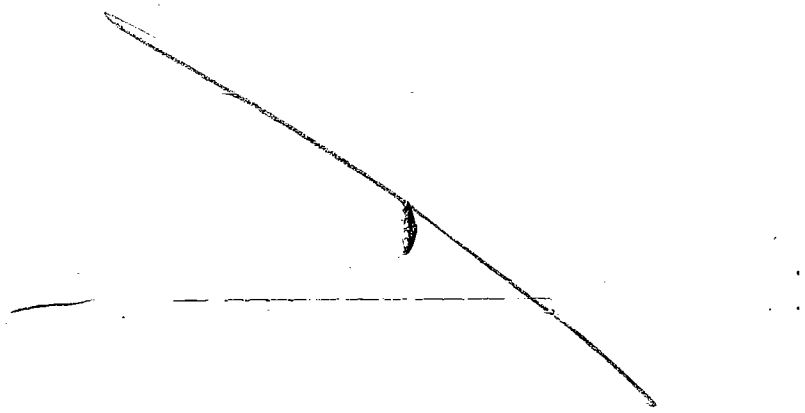
_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Conclusions

The sponsor has adequately assessed both the in vivo and in vitro performance of the proposed fluocinolone acetonide implant dosage form. The proposed labeling revision should be forwarded to the sponsor for inclusion in their package insert.

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____



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_____ § 552(b)(4) Trade Secret / Confidential

6 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-737	Brand Name	RETISERT
OCPB Division (I, II, III)	III	Generic Name	Fluocinolone Acetonide
Medical Division	HFD-550	Drug Class	Corticosteroid
OCPB Reviewer	Bashaw	Indication(s)	Posterior Uveitis
OCPB Team Leader	Bashaw	Dosage Form	Intravitreal Implant
		Dosing Regimen	1 (0.59mg) q 30 MONTHS
Date of Submission	10/8/04	Route of Administration	Intraocular
Estimated Due Date of OCPB Review	1/30/05	Sponsor	Bausch & Lomb
PDUFA Due Date	4/8/05	Priority Classification	1-P, CMA
Division Due Date	2/20/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**YES**	
Comments sent to firm ?	**No**	
QBR questions (key issues to be considered)		**1.) As the plasma levels (n=156) were below the limit of detection (200pg/ml) was the assay properly validated?** **2.) When required, a number of implanted "tablets" were removed, these "tablets" were analyzed for residual drug content, what was the residual drug content and was there a relationship between residual and duration of implant?** **3.) Are the in vitro drug release specifications adequate?**
Other comments or information not included above		
Primary reviewer Signature and Date	**EDB 12/1/04**	
Secondary reviewer Signature and Date		

CC: NDA 21-737, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-550(CSO-Rodriquez), HFD-880(TL, DD, DDD), CDR

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

/s/

Dennis Bashaw
2/25/05 09:59:10 AM
BIOPHARMACEUTICS

Arzu Selen
2/28/05 12:07:40 PM
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