CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-493

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Gatifloxacin
PRODUCT (Brand Name):	[redacted]
DOSAGE FORM:	Ophthalmic solution
DOSAGE STRENGTHS:	Gatifloxacin 0.3%
INDICATION:	Treatment of bacterial conjunctivitis
NDA:	21-493
NDA TYPE:	S
SUBMISSION DATE:	5/30/02
SPONSOR:	Allergen Inc.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Dennis Bashaw, Pharm.D.
OCPB DIVISON:	DPE III, HFD 880
OND DIVISION:	ODE V, HFD 550

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The dosing in this study is as follows:

Day 1: 2 drops/eye once only
Day 2-8: 2 drops/eye four times daily
Days 9-11: 2 drops/eye eight times daily

Blood samples were collected during the repeated dose portion of the study at predose on day 2, and at 0.5, 1, and 2 hours after the 4 th dose on days 5 and 8. Blood samples were collected during the frequent dosing portion of the study at predose on day 9 and at 0.5, 1, 2, and 12 hr after the 8 th dose on day 11.

Serum gatifloxacin concentrations were measured using an HPLC method, and were uniformly below the lower limit of detection in ALL subjects. This LOQ is the same as that used for oral gatifloxacin, hence, quantifiable concentrations of gatifloxacin after topical ocular dosing would not be expected. However, considering that the dose for ophthalmic use is drastically lower than that for oral or IV use, systemic safety would not be a concern after ocular dosing.

RECOMMENDATION

The Clinical Pharmacology and Biopharmaceutics section of the NDA 21-493 is acceptable from the standpoint of the Office of Clinical Pharmacology and Biopharmaceutics, provided the following labeling changes are incorporated in the final label.

LABELING RECOMMENDATION

The following labeling changes in the "Pharmacokinetics" section under "CLINICAL PHARMACOLOGY" section of the label should be conveyed to the sponsor.

Pharmacokinetics: Gatifloxacin ophthalmic solution, was administered to one eye of 6 healthy male subjects in an escalated dosing regimen starting with a single 2 drop dose, then 2 drops 4 times daily for 7 days and finally 2 drops 8 times daily for 3 days. At all time points, serum gatifloxacin levels were below the lower limit of quantification (5 ng/mL) in all subjects.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

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

APPENDIX
FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-493	Brand Name	[redacted]
OCPB Division (I, II, III)	III	Generic Name	Gatifloxacin
Medical Division	550	Drug Class	Broad spectrum fluroquinolone
OCPB Reviewer	Tandon	Indication(s)	Bacterial Conjunctivitis
OCPB Team Leader	Bashaw	Dosage Form	Ophthalmic Solution
		Dosing Regimen	1 drop 4-8 times daily
Date of Submission	May 30, 2002	Route of Administration	Topical
Estimated Due Date of OCPB Review	August 30, 2002	Sponsor	Allergan
PDUFA Due Date	November 30, 2002	Priority Classification	3S
Division Due Date			

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.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1	1	
Patients-				
single dose:				
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	1	

Filability and QBR comments		
I.	"X" if yes	Comments
II. Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
III. Comments sent to firm ? IV.		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is Gatifloxacin absorbed after topical ophthalmic application, if yes, low are the levels compared to oral and IV administration.**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Veneeta Tandon, 6/24/02**	
Secondary reviewer Signature and Date	**Dennis Bashaw, 6/24/02**	

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

/s/

Veneta Tandon
8/1/02 10:34:13 AM
BIOPHARMACEUTICS

Dennis Bashaw
8/1/02 07:35:01 PM
BIOPHARMACEUTICS