

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-664

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

bromfenac ophthalmic solution (0.1%) dosing regimen. Given the fact that bromfenac is not a new molecular entity and there is prior PK knowledge for this compound via other administration routes, additional pharmacokinetic studies using a validated and more sensitive analytical method are not likely to provide additional information. From a Clinical Pharmacology and Biopharmaceutics perspective, a waiver of *in vivo* bioavailability studies under the "good cause" provisions of 21CFR320.22(e) can be granted, to avoid conducting unnecessary studies in humans.

Recommendations for consideration for the final labeling are included in the Labeling section (Pages 4-5).

Background

Bromfenac is a Non-Steroidal Anti-inflammatory Drug (NSAID) that, when administered systemically, has demonstrated analgesic, anti-inflammatory, and antipyretic activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclo-oxygenase 1 and 2. An oral dosage form of bromfenac (25 mg capsule) was approved in 1997 (NDA 20-535), and later was withdrawn by Wyeth due to liver toxicity in 1998. Although withdrawn from the market, the Wyeth NDA is still technically approved-but not marketed.

This NDA is for an ophthalmic solution (0.1%) dosage form of bromfenac sodium. The indication as proposed by the Sponsor is for the treatment of postoperative inflammation _____ in patients who have undergone cataract extraction. The proposed dosage is one drop applied to the affected eye(s) two times daily beginning 24 hours after cataract surgery and continuing through the first two weeks of the postoperative period. Because the Wyeth NDA is still "approved", this sponsor was able to obtain from Wyeth a "right of reference" for the NDA allowing this sponsor to directly access and utilize the data contained in the Wyeth application. Thus, this application is a 505 (b)(1) application. The proposed ophthalmic formulation was developed by Senju Pharmaceuticals, Co., Ltd. and is currently approved for commercial use in Japan (approved in 2000). The Sponsor of this NDA licensed Xibrom (bromfenac) ophthalmic solution from Senju and conducted two double-masked, randomized, placebo-controlled Phase 3 studies in the U.S. to support the approval of this product in the U.S..

The Sponsor submitted two studies to fulfill the *in vivo* bioavailability/bioequivalence requirement: Study F-27 (conducted in 1989) and Study G-01 (conducted in 1991-1992). Both studies were conducted by Senju. Study F-27 is a metabolic disposition study of ¹⁴C-bromfenac in healthy volunteers after a single 50 mg dose of bromfenac as a sodium salt. Study G-01 is a Phase 1 clinical study of bromfenac sodium ophthalmic solution (0.1% and 0.2%) administered twice daily for 28 days in Japanese healthy subjects. Although study reports were provided, but the analytical methods for these studies were not validated and analytical reports were not available. Therefore, these studies could not be used to fulfill the *in vivo* bioavailability/bioequivalence requirement under 21CFR320 for this NDA.

The following comments were conveyed to the Sponsor during the filing:

The study reports submitted to the human pharmacokinetics section could not be reviewed because analytical methods for these studies were not validated and analytical reports were not available. These studies will not fulfill the in vivo bioavailability/bioequivalence requirement under 21CFR320. However, based on the dosing of bromfenac ophthalmic solution (0.1%) and prior PK knowledge of

bromfenac, systemic exposure of bromfenac is projected to be below the limit of quantification from the literature [redacted]. Additional in vivo pharmacokinetic studies using a validated and more sensitive analytical method are not likely to provide additional information. Based on this information a waiver of evidence of in vivo bioavailability or bioequivalence would be possible under the provisions of 21CFR320.22.

Following this communication, the Sponsor submitted a request for a Waiver of Evidence of *In Vivo* Bioavailability on July 7, 2004.

Drug Substance and Drug Product

Drug Substance: Bromfenac Sodium

Empirical Formula	C ₁₅ H ₁₁ BrNNaO ₃ • 1½H ₂ O
Molecular Weight	383.17
Chemical Names	2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate
Appearance	Yellow to orange crystalline powder
Structure	

Drug Product:

Bausch & Lomb Pharmaceuticals, Inc., in Tampa, FL, will manufacture Xibrom (bromfenac sodium) ophthalmic solution, 0.1% for commercial use. The quantitative composition of the drug product is in Table 1. There has been no formulation modification during the Phase 2 and 3 studies in Japan and the U.S.. It is also the same formulation as the one currently marketed in Japan.

Table 1. Drug Product Quantitative Composition.

Components	Function	Amount/mL
Bromfenac sodium hydrate		0.001035 g*
Boric acid		[redacted]
Sodium borate		[redacted]
Sodium sulfite, Anhydrous		[redacted]
Disodium edetate		[redacted]
Povidone		[redacted]
[redacted]		[redacted]
Polysorbate 80		[redacted]
Benzalkonium chloride solution		[redacted]
Sodium hydroxide		[redacted]
Purified Water		[redacted]

Waiver Request

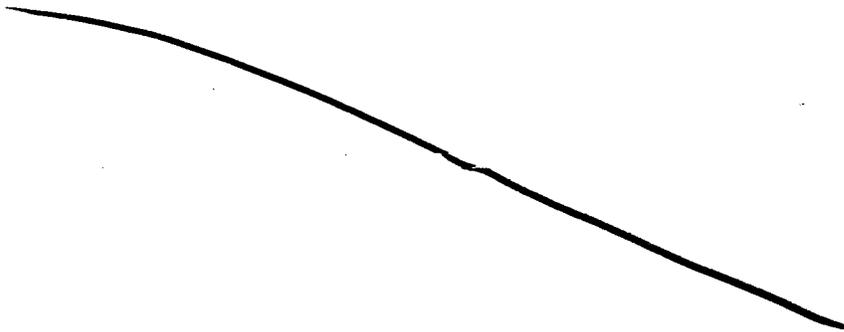
The waiver of *in vivo* bioavailability studies is based upon the lack of feasibility in quantifying bromfenac in the plasma following ophthalmic application. This finding is based partially on the following estimation:

The drug dose will be 1 drop to the affected eye(s) with a BID regimen for 2 weeks. As 1 drop is approximately 1/20 mL (50 μ L), the maximum dose (1 drop to each eye) will be ~ 0.1 mg per dose [=1 mg/mL (0.1% solution) * (1/20) mL * 2 eyes]. The reported oral bioavailability, apparent terminal half-life, and volume of distribution of bromfenac are approximately 67%, 1.3 hr and 0.15 L/kg (or 10.5 L for a 70 kg human), respectively¹. If we assume 100% bioavailability and instantaneous absorption from the eyes, the predicted peak plasma levels of a single (one drop to each eye) would be approximately 10 ng/mL (=0.1 mg/10.5 L). If we assume terminal half-life of bromfenac is the same after topical administration as that after oral administration (i.e., 1.3 hr), accumulation after multiple doses would be minimum (~ 1) at steady state based on a BID dosing regimen, i.e., peak plasma concentrations at steady state would be similar to peak plasma concentrations after a single dose. Based on the above estimation, the projected peak plasma levels (~ 10 ng/mL) after either single or multiple doses are far lower than those measured in oral studies (in μ g/mL ranges with doses of 25-75 mg). In Study G-01 conducted by Senju, bromfenac plasma concentrations were below the limit of quantification (██████████) at all timepoints, confirming that bromfenac plasma levels are low.

Because bromfenac is not a new molecular entity, there is prior human PK knowledge for this compound via other administration routes using significantly higher doses. It is estimated that systemic exposure of bromfenac will be below the limit of quantification (██████████) with the proposed ophthalmic solution (0.1%) dosing for his product. Additional pharmacokinetic studies using a validated and more sensitive analytical method are not likely to provide additional information. In response to the Sponsor's waiver request, a waiver of evidence of *in vivo* bioavailability or bioequivalence studies under 21CFR320.22(e) to this NDA application can be granted.

Labeling

Recommendations for changes to the proposed labeling are provided below (only affected sections relating to **Clinical Pharmacology** are listed).



¹ Skjodt N and Davies N, Clinical pharmacokinetics and pharmacodynamics of bromfenac. *Clin Pharmacokinet*, 36(6):399-408 (1999).

SIGNATURE OF REVIEWER: <u>Lei Zhang</u>	Date <u>3/8/2005</u>
SIGNATURE OF TEAM LEADER: <u>E. Dennis Bashaw</u>	Date <u>3/8/2005</u>
CC.: HFD # [880]; TL: [Dennis Bashaw]; DD: [John Lazor]; DDDD [Arzu Selen]	Project Manager: <u>Raphael Rodriguez</u> Date _____

Appendix 1. Proposed Labeling from the Sponsor (P. 6-10)

Appendix 2. OCPB Filing and Review Memo (P. 11-12)

5 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

Appendix 2. OCPB Filing and Review Memo

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

General Information About the Submission

	Information		Information
NDA Number	21-664	Brand Name	Xibrom™
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Bromfenac Sodium
Medical Division	DAAODP (HFD-550)	Drug Class	NSAID
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	For the treatment of postoperative inflammation in patients who have undergone cataract extraction
OCPB Team Leader	Dennis Bashaw, Pharm. D.	Dosage Form	0.1% Ophthalmic Solution
		Dosing Regimen	BID (one drop to the affected eye) beginning 24 hr after cataract surgery and continuing through the first 2 weeks of postoperative period
Date of Submission	5/24/2004	Route of Administration	Topical ocular
Estimated Due Date of OCPB Review	2/15/2005	Sponsor	ISTA Pharmaceuticals
PDUFA Due Date	3/26/2005	Priority Classification	New Dosage Form (3-S)
Division Due Date			IND 60, 295

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			
man PK Summary	X			
relating	X			
Reference Bioanalytical and Analytical Methods				Analytical methods were not validated and reports are not available
I. Clinical Pharmacology				
Mass balance:	X	1		F-27 (oral)
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1		Study G-01 (in Japanese healthy volunteers)
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	X			
Total Number of Studies		2	0	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?		•		
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> Based on the known PK information of bromfenac, is additional PK studies with a validated and more sensitive analytical methods needed for this application? Can a waiver for in vivo BA/BE be granted? 			
Other comments or information not included above	<p>The following comments were submitted to the Sponsor during filing:</p> <p><i>The study reports submitted to the human pharmacokinetics section could not be reviewed because analytical methods for these studies were not validated and analytical reports were not available. These studies will not fulfill the in vivo bioavailability/bioequivalence requirement under 21CFR320. However, based on the dosing of bromfenac ophthalmic solution (0.1%) and prior PK knowledge of bromfenac, systemic exposure of bromfenac is projected to be below [REDACTED]. Additional pharmacokinetic studies using a validated and more sensitive analytical method are not likely to provide additional information. Based on this information, should the sponsor request a waiver, then the Agency would grant a waiver of evidence of in vivo bioavailability or bioequivalence under 21CFR320.22(e) to this NDA application.</i></p> <p>In response, the Sponsor submitted a biowaiver request on July 7, 2004.</p>			
Primary reviewer Signature and Date	Lei Zhang, 7/21/2004			
Secondary reviewer Signature and Date	Dennis Bashaw, 7/28/2004			

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this page is the manifestation of the electronic signature.**

/s/

Lei Zhang
3/8/05 02:03:21 PM
BIOPHARMACEUTICS

Dennis Bashaw
3/8/05 02:57:27 PM
BIOPHARMACEUTICS