CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-165

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-165 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cambia Established/Proper Name: diclofenac Dosage Form: powder for oral solution		Applicant: Kowa Pharmaceuticals Agent for Applicant (if applicable):
RPM: Lana Y. Chen		Division: Neurology

NDAs: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 20-142 Cataflam (diclofenac potassium) and NDA 19-201, 20-254 Voltaren (diclofenac sodium) Provide a brief explanation of how this product is different from the listed drug. dosage form ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☒ No changes ☐ Updated Date of check: 9/28/09 **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	6/17/09
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 10/27/08
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: Pediatric Studies deferred : ages 12-17	11/7/08
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	YES
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☐ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 6/17/09; CR 10/27/08
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	See AP Letter 6/17/09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

[3] Fill in blanks with dates of reviews, letters, etc.

• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	See CR Pkg OSE/DMEPA Review 4/24/09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	See AP Pkg
❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable 11/19/08
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Feb 13, 2007
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None
Division Director Summary Review *(indicate date for each review)*	☐ None 5/26/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 6/16/09
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	6/16/09
• Clinical review(s) *(indicate date for each review)*	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None April 13, 2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 5/30/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
Product Quality ☒ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) *(indicate date for each review)*	☐ None
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
• BLAs: ○ TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation

○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

1.3.5 Patent and Exclusivity

1.3.5.1 Patent Information

An image of the signed Patent Information form, Form FDA 3542a, is attached.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-165

NAME OF APPLICANT / NDA HOLDER
ProEthic Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To be Determined

ACTIVE INGREDIENT(S)	STRENGTH(S)
diclofenac potassium	50 mg

DOSAGE FORM
Powder for Oral Solution in dosage unit (Sachet)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,974,595	12/13/2005	05/15/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
ProEthic Pharmaceuticals, Inc.	212 South Tryon Street - Suite 1280	
	City/State: Charlotte, NC	
	ZIP Code: 28281	FAX Number *(if available)*: (704) 831-6304
	Telephone Number: (704) 831-6298	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Clark G. Sullivan	Arnall Golden Gregory, 171 17th Street NW	
	City/State: Atlanta, GA	
	ZIP Code: 30363	FAX Number *(if available)*: (404) 873-8513
	Telephone Number: (404) 873-8512	E-Mail Address *(if available)*: clark.sullivan@agg.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☑ Yes	☐ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* Use Code U-436 - Acute Treatment of Migraine Attacks with or without Aura in Adults		

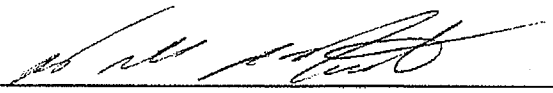
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	5/4/07

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☑ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name William Maichle	
Address 212 South Tryon Street, Suite 1280	City/State Charlotte, NC
ZIP Code 28281	Telephone Number (704) 831-6298
FAX Number *(if available)* (704) 831-6304	E-Mail Address *(if available)*

1.3.5.2 Patent Certification

Reference Listed Drugs – Diclofenac as the Sodium and Potassium Salts:

A search within the electronic Orange Book data base disclosed the following Patent and Exclusivity Search Results. No unexpired patents were found from queries on the following Reference Listed Drug listings with direct applicability to Product PRO-513:

1) Application No. 020142 Product 002 in the OB_Rx list (Diclofenac Potassium Tablet: Oral Cataflam, Novartis);

2) Application No. 019201 Product 003 in the OB_Rx list (Diclofenac Sodium Tablet, Delayed Release Oral Voltaren, Novartis); or

3) Application No. 020254 Product 001 in the OB_Rx list (Diclofenac Sodium Tablet, Delayed Release Oral: Voltaren-XR, Novartis).

Other Diclofenac Products:

There are no other approved drug products on which investigations are relied upon for this application.

In Regards to PRO-513:

ProEthic certifies that to the best of its knowledge and belief the only U.S. patent that claims the Drug Product PRO-513, is patent 6,974,595 issued from the US Patent and Trademark office, which patent relates to the drug product's Method of Use (see section 1.3.5.1 for Form FDA 3542a). Patent 6,974,595 is owned by ProEthic and information concerning this patent has been submitted to the FDA with a Product Use Code of U-436 - ACUTE TREATMENT OF MIGRAINE ATTACKS WITH OR WITHOUT AURA IN ADULTS

Under IND 73,073 ProEthic has conducted Phase III research which it believes to be sufficient to support the market approval of a new buffered powder dosage formulation of the product, PRO-513 (50 mg Diclofenac Potassium Powder for Oral Solution), for the Acute Treatment of Migraine Attacks with or without aura, in which it holds this intellectual property position.

1.3.5.3 Exclusivity Request

Statement of Claimed exclusivity:

Pursuant to a license granted by Applied Pharma Research SA, ProEthic Pharmaceuticals Inc. (here-in-after referred to as ProEthic) commenced development of PRO-513 (50 mg Diclofenac Potassium Powder for Oral Solution), under IND 73,073. PRO-513 is a new formulation of an approved chemical entity (Cataflam - NDA 20-142) it is a prescription medication whose intended use is the acute treatment of migraine attacks, with or without aura, in adults. Under the licenseing agreement ProEthic obtained the right to use certain data from a double-blind, placebo-controlled, Phase-III clinical trial conducted in Europe by Novartis Pharmaceuticals SA, of the formulation (Trial CAT458C2301) and a pharmacokinetic trial wherein the packet powder dosage forms pharmacokinetics was compared to the European marketed diclofenac potassium tablet (Trial CAT458C2101). Following a literature search and a Pre-IND meeting with the FDA it became apparent that an additional Phase-III safety and efficacy trial would be necessary prior to ProEthic submitting a market application.

FDA approval to market the new powder formulation coupled with a new indication for use, Migraine Attack, is now being sought by ProEthic through a 505(b)(2) NDA.

ProEthic claims marketing exclusivity for PRO-513 for the term of three (3) years from the date of approval, pursuant to 21 CFR 314.50 (j) (1). This claim is based upon ProEthic's seeking marketing approval for the PRO-513 dosage formulation for an unapproved indication for the drug substance diclofenac as the potassium salt, the Acute Treatment of Migraine Attack with or without Aura.

The 3 year market exclusivity claim is supported by the following facts stated pursuant to 21 CFR 314.108(b)(4)(iii) and (iv): 1) ProEthic states that the drug product contains an active moiety, diclofenac as the potassium salt, that was previously approved as both potassium and sodium salts in tablet dosage forms marketed under NDA 20-142 and NDA 19-201, respectively; and 2) the NDA 22-165 contains reports of new clinical investigation sponsored by ProEthic and conducted under ProEthic IND number 73,073, PRO-513 (50 mg Diclofenac Potassium Powder for Oral Solution). ProEthic is listed as Sponsor on IND 73,073 Form FDA 1571. Under IND 73,073, in addition to a pharmacokinetic study (PRO-513101), an additional new clinical investigation (PRO-513301) of safety and efficacy was conducted that study being necessary to seek approval of the application.

Pursuant to 21 CFR 314.50(j)(4)(i) and (ii), ProEthic certifies, to the best of applicant's knowledge, that each of the two clinical investigations conducted as protocols PRO-513301 and CAT458C2302, included in the application meets the definition of a "new clinical investigation" as set forth in 21 CFR 314.108(a). These studies are considered essential to approval of the product PRO-513 as a treatment for migraine attack as they are the only two well controlled studies.

EXCLUSIVITY SUMMARY FOR NDA # _____22-165__ SUPPL #_____

Trade Name _Cambia_____Generic Name _diclofenac___

Applicant Name Kowa Pharmaceuticals HFD#120

Approval Date If Known ___6/17/09_

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_____505(b)2_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /__X_/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 YEARS_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# __20-809_ _____ Diclofenac Eye Drops_____

NDA# __21-234 Diclofenac CR Patch

NDA# __22-122_____ _____Voltaren Gel_____

NDA# 20-142 CATAFLAM TABLET

NDA# 19-201 VOLTAREN DELAYED RELEASE TABLET

NDA# 20-254 VOLATREN-XR DELAYED RELEASE TABLET

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__x_/

If yes, explain:

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Efficacy Study PRO-513301

_____

Efficacy Study CAT458C2301

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /__ _/ NO /_X__/

Investigation #2 YES /__ _/ NO /__X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /__X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

[Please add names of pivotal efficacy studies identified in reviews]

Efficacy Study PRO-513301

Efficacy Study CAT458C2301

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /_x__/ ! NO /___/ Explain: _____

!

!

Investigation #2 !

!

IND # _____ YES /_x__/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x__/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22165	ORIG-1	KOWA PHARMACEUTICALS AMERICA INC	PRO 513

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/s/

LANA Y CHEN
03/04/2010

RUSSELL G KATZ
03/11/2010

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 18, 2010

TO: Russel Katz, MD, Director
Division of Neurological Products

THROUGH: Suzanne Barone, Ph. D. Team Leader
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

FROM: Kendra Biddick,
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

SUBJECT: Cambia (diclofenac, NDA 22-165) Change in sponsor and request for REMS modification.

This memorandum provides comments on the request for modification of the REMS for Cambia(diclofenac), dated January 28, 2010 because of a change in the drug's sponsor and delay of marketing.

BACKGROUND

In 2007, the Food and Drug Administration Amendments Act (FDAAA) granted the FDA authority to require risk evaluation and mitigation strategies (REMS) to help ensure that the benefits of a drug outweigh the risks. FDAAA also gave the FDA additional enforcement tools including misbranding charges and civil penalties for sponsors that do not follow requirements of an approved REMS.

Cambia was approved for the acute treatment of migraine attacks with or without aura in adults. It carries a boxed warning concerning an increased risk of cardiovascular and gastrointestinal adverse events. Because of these concerns, this drug was approved with a REMS on June 17, 2009. The sponsor was Kowa Pharmaceuticals America.

The goal of the REMS is to inform patients about the serious risks associated with the use of CAMBIA, particularly the increased risk of cardiovascular events and gastrointestinal toxicity.

The REMS Elements include:

1. Medication Guide, included as part of secondary packaging of unit of use package
2. Timetable for Assessments. The Timetable for Assessments that was approved June 17, 2009 follows:

> Assessment of the REMS will be performed as follows:
> Assessment Protocol* Submission to FDA: On or before the end of October 2010,
> 1st FDAAA assessment: On or before the end of December 2010,
> 2nd FDAAA assessment: On or before the end of June 2012,
> 3rd FDAAA assessment: On or before the end of June 2016.
> Kowa will submit the final assessment reports within 60 days from the close of the above projected assessment periods.

Summary of Request for REMS Modification

On December 11, 2009 Nautilus Neurosciences, Inc. notified the FDA that NDA 22-165 was transferred from Kowa Pharmaceuticals to Nautilus effective November 24, 2009, and that Nautilus Neurosciences would be submitting proposed revised dates for REMS and Pediatric Assessment requirements. On January 28, 2010, Nautilus Neurosciences, Inc. submitted a request to modify the REMS, including a proposal to extend the entire Timetable For Assessments for one year because they do not intend to launch the drug until June 2010.

Office of Compliance Recommendations

FDCA section 505-1(d) states that the minimal strategy is a timetable for assessments which are to occur 18 months, 3 years, and within the 7th year "after the strategy is initially approved" This is a statutory requirement. OC recommends that the 18 month assessment be submitted on time by December 17, 2010. However, the content of that assessment can be modified to be a status report. An additional assessment can be added for June 17, 2011 if the FDA wants the information about patient's understanding of the medication guide before 2012.

OC requests that the Timetable for Assessments be modified to read as follows:

> First REMS assessment is due: December 17, 2010
> Second REMS assessment is due: June 17, 2012
> Third REMs assessment is due: June 17, 2016
>
> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the

submission date for that assessment. Nautilus Neurosciences, Inc. will submit each assessment so that it will be received by the FDA on or before the due dates listed above.

OC also recommends that the sponsor be reminded that a REMS assessment is required whenever a modification to a REMS is requested (section 505-1(g)(2)), and that each REMS assessment should include a status report on any postapproval studies required under section 505(o) or otherwise undertaken by the responsible person to investigate a safety issue, the status of such study, including whether any difficulties completing the study have been encountered; and any clinical trials required under section 505(o). Refer to section 505-1(g)(3)(B) and (C).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22165	SAFETYRPT-2	KOWA PHARMACEUTICALS AMERICA INC	PRO 513

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/s/

HALEY H SEYMOUR
03/19/2010

Chen, Lana Y

From: Greeley, George
Sent: Wednesday, March 17, 2010 3:33 PM
To: Chen, Lana Y
Cc: Stowe, Ginneh D.
Subject: NDA 22-165 Cambia

Importance: High

Hi Lana,

The Cambia (diclofenac) partial waiver and deferral and plan was reviewed by the PeRC PREA Subcommittee on November 19, 2008.

The Division recommended a partial waiver for pediatric patients 0-5 years because there are too few children with disease/condition to study and a deferral from 6 years to 17 years of age because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a partial waiver for this product but will need a pediatric plan with the timelines before approval of this application.

The pediatric plan for deferrals MUST include a brief description of studies in addition to:

1. *Protocol Submission Date*
2. *Study Completion Date*
3. *Final Report Submission Date*

The PeRC also recommends that the Division uncheck the "need additional adult safety or efficacy data" on the neonate line of the deferral section.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

FDA Center for Drug Evaluation and Research
Division of Neurology Products, HFD-120

MEMORANDUM

DATE:	May 26, 2009
TO:	Russell Katz, M.D. Director Division of Neurology Products HFD-120
THROUGH:	Eric Bastings, M.D. Deputy Director Division of Neurology Products HFD-120
FROM:	Nushin Todd, M.D., Ph.D. Medical Officer Division of Neurology Products
APPLICATION/DRUG:	NDA: 22-165 Drug Name: Cambia Indication: For acute treatment of migraine Sponsor: Kowa Pharmaceuticals America, Inc
SUBJECT:	Complete response and resubmission of NDA 22-165 following FDA Complete Response letter dated 27 October 2008

On September 28, 2007, the Division of Neurology Products (DNP) received a new drug application (NDA) for diclofenac potassium powder for oral solution for the treatment of acute migraine attacks in adults (NDA 22-165). The product (PRO-513, with proposed trade name Cambia) is a sachet containing 50 mg of diclofenac potassium powder, which will be mixed with 1-2 ounces of water immediately prior to an oral administration for the acute treatment of migraine. The original submission was from ProEthic Pharmaceuticals, Inc., but as of September 1, 2008, ProEthic changed its name to Kowa Pharmaceuticals America, Inc. and assumed responsibility for all sales and marketing functions operating in the U.S.

On October 27, 2008, DNP issued a Complete Response (CR) letter due to the following outstanding issues:

- More literature data was needed to assess reproductive / developmental toxicity, which might impact the nonclinical sections of labeling.
- Risk Evaluation and Mitigation Strategy (REMS) with a Medication Guide needed to be submitted.

The NDA was resubmitted in response to the CR letter on December 12, 2008. The resubmission was classified as Class 2 (6-month review goal) with PDUFA due date on June 17, 2009.

Conclusions and Recommendations:
No new clinical information has been submitted since the CR letter which was for non-clinical reasons. From a clinical standpoint, there are no new clinical data, and no new clinical issues against the approval of the product.

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/s/

Nushin Todd
6/17/2009 11:57:55 AM
MEDICAL OFFICER

Russell Katz
6/19/2009 07:54:43 AM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: June 8, 2009

To: Eric Bastings, M.D., Team Leader
Division of Neurology Products

CC: Lana Chen, RPh, Project Manager
Division of Neurology Products

Mary Dempsey, Project Management Officer
OSE – Division of Risk Management

Jodi Duckhorn, MA, Team Leader
OSE – Division of Risk Management

Robin Duer, RN, MBA, Patient Product Information Reviewer
OSE – Division of Risk Management

From: Sharon Watson, PharmD, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: Cambia (Diclofenac Sachet for Oral Solution) NDA: 22-165

DDMAC has reviewed the proposed Medication Guide (Med Guide) for Cambia as edited in the May 13, 2009, review from OSE's Division of Risk Management. We offer the following comments. If you have any questions or concerns regarding these comments, please contact me.

- **TITLE**
  - *"CAMBIA (diclofenac potassium **for oral solution**)"* [emphasis added]
    - This is inconsistent with the drug name in the proposed product labeling (PI), which states, "Cambia™ (b) (
- **WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT CAMBIA?**

- *"CAMBIA, which contains diclofenac, (a non-steroidal anti-inflammatory drug or NSAID), may increase your chance of a heart attack or stroke that can lead to death. This risk is higher . . . in people who have heart disease."*
  - This section omits important risk information from the boxed warning in the proposed PI, which states, "Patients with cardiovascular disease **or risk factors for cardiovascular disease** may be at greater risk" and information from the WARNINGS AND PRECAUTIONS section of the proposed PI which states, "Patients with known CV disease **or risk factors for CV disease** may be at greater risk." [emphasis added] Please consider including this information, including a list of risk factors, in this section. For example, we note that the Med Guide for Treximet states, "**Treximet is not recommended for people with risk factors for heart disease unless a heart exam is done and shows no problems.**" The Med Guide for Treximet also includes a list of risk factors for heart disease such as hypertension, high cholesterol, smoking, etc.

- **HOW SHOULD I TAKE CAMBIA?**
  - *"Take 1 dose of CAMBIA to treat your migraine headache."*
    - This section does not discuss whether patients should take Cambia with or without food. We note that the DOSAGE AND ADMINISTRATION, FOOD EFFECT section of the proposed PI states, "Taking Cambia with food may cause a reduction in effectiveness compared to taking Cambia on an empty stomach."
    - If taking Cambia with or without food is clinically important for safety or effectiveness, please include this information in this section.

- **BEFORE YOU TAKE CAMBIA, TELL YOUR HEALTHCARE PROVIDER ABOUT ALL YOUR MEDICAL CONDITIONS**
  - *"including if you: have . . ."*
    - This section of the proposed Med Guide fails to fully instruct patients about the risk of gastrointestinal effects and risk of ulceration, according to the WARNINGS AND PRECAUTIONS, 5.2 GASTROINTESTINAL EFFECTS section of the proposed PI. The proposed PI states, "NSAIDS, including diclofenanac, should be prescribed with extreme caution in those patients with a **prior history of ulcer disease or gastrointestinal bleeding**. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDS, have a greater than 10-fold

risk for developing a GI bleed than patients with neither of these risk factors." Please include instruction in this section for patients with a history of ulcer disease or gastrointestinal bleeding to notify their healthcare provider.

- **TELL YOUR DOCTOR ABOUT ALL THE MEDICINES YOU TAKE**
  - "*Especially tell your doctor if you take* . . ."
    - This section omits other drugs with interactions described in the DRUG INTERACTIONS section of the proposed PI, such as ace inhibitors, thiazide diuretics, furosemide, lithium, methotrexate, and cyclosporine. If these drug interactions are clinically relevant, please consider including them in this section in consumer-friendly language.
    - This section also omits the risk information from the WARNINGS AND PRECAUTIONS, HYPERTENSION section of the proposed PI, which states, "Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Cambia, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy." Please consider including this information in the Med Guide.

- **WHAT ARE THE POSSIBLE SIDE EFFECTS OF CAMBIA?**
  - *"Serious side effects include: . . ."*
    - This section omits important information from the 5.14 LABORATORY TESTS section of the proposed PI, which states, "Patients on long-term treatment with NSAIDs, including Cambia, should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, Cambia should be discontinued." Please consider including this information in the Med Guide.
  - "*high blood pressure*"
    - This section omits the important risk information from the WARNINGS AND PRECAUTIONS 5.4 HYPERTENSION section of the proposed PI, which states, "Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy."
  - *"kidney problems including kidney failure"*
    - This section omits the risk information from the WARNINGS AND PRECAUTIONS 5.6 RENAL EFFECTS section of the proposed PI, which states, "Caution should be used when initiating treatment with Cambria in patients with considerable dehydration" and "Patients at greatest risk of this reaction are those with impaired renal function, heart

failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly." Please consider adding more information regarding this risk here.

- *"liver problems including liver failure"*
  - This section omits the risk of **fatality or liver transplantation**, as described in the WARNINGS AND PRECAUTIONS 5.3 HEPATIC EFFECTS section of the proposed PI. Please include the risk of fatality or liver transplantation in this section.
  - This section omits the need for periodic measurement of transaminase levels in patients receiving long-term therapy with diclofenac, as described in the WARNINGS AND PRECAUTIONS 5.3 HEPATIC EFFECTS section of the proposed PI. Since severe hepatotoxicity may develop **without a prodrome of distinguishing symptoms, this is especially important information for consumers to know.**
  - In addition, this section omits the precautions from this section of the proposed PI, "Caution should be exercised in prescribing Cambia with concomitant drugs that are known to be potentially hepatotoxic (e.g. **acetaminophen, certain antibiotics, antiepileptics**). Patients should be cautioned to avoid taking unprescribed acetaminophen while using Cambia." Please consider including this information here.
- This section of the proposed Med Guide currently lists only nausea and dizziness as common side effects. If there are other common side effects associated with the use of Cambia, please consider adding them to this section.

- **GENERAL COMMENTS**
  - Please note that there are editorial/grammatical errors in section 8.1 of the proposed PI.

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/s/

Sharon Watson
6/8/2009 04:01:50 PM
DDMAC CONSUMER REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Director, DDMAC, HFD-042**
Attention: Amy Toscano

FROM:
Eric Bastings, MD
Team Leader, Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 26, 2009		22-165	REMS/MedGuide	November 12, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
Cambia (Diclofenac Sachet for Oral Solution)		Migraine	June 6, 2009

NAME OF FIRM: Kowa

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: **Risk Evaluation and Mitigation Strategy (REMS).** Clinical Team Leader is Eric Bastings 6-1039. The network location is : \\CDSESUB1\EVSPROD\NDA022165\022165.ENX

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Lana Chen, RPh, Project Manager 301-796-1056	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Eric Bastings

5/27/2009 03:07:50 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-170/ DAARP:
Sharon Hertz, M.D., Deputy Director, DAARP

FROM: HFD-120 (Division of Neurology Products)
X_____
Eric Bastings, MD, Clinical Team Leader

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
March 9, 2009		22-165	NDA Resubmission	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Diclofenac Sachet for Oral Soln		Migraine	April 7, 2009

NAME OF FIRM: Kowa

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☒ OTHER: Original NDA	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please see attached DNP proposed labeling for a diclofenac 505(b)(2) for the treatment of migraine. A CR action was taken on 10/27/08. Class 2 Resubmission goal date (6 mo clock) is June 17, 2009.

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one):
Lana Yan Chen, PM 6-1056	☐ MAIL ☒ HAND

15 pgs withheld after this page as B4 (Draft Labeling)

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/s/

Eric Bastings

3/9/2009 04:52:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION
TO (Division/Office) **Maternal Health Team**	**FROM:** **HFD-120/NEUROLOGY PRODUCTS** **X_____** **Eric Bastings, MD, Clinical Team Leader**

Date	IND No.	NDA No.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 9, 2009		22-165	Resubmission	Dec 12, 2008

NAME OF DRUG: Diclofenac

NAME OF DRUG COMPANY: Kowa

INDICATION OF DRUG: Migraine

DESIRED COMPLETION DATE: April 7, 2009

REASON FOR REQUEST

Please see attached DNP proposed labeling for diclofenac 505(b)(2) for the treatment of migraine. A CR action was taken on 10/27/08. Class 2 Resubmission goal date (6 mo clock) is June 17, 2009.

SIGNATURE OF REQUESTER: Lana Yan Chen, PM 6-1056	METHOD OF DELIVERY (CHECK ONE) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

10 pages withheld after this page as B4 (Draft Labeling)

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/s/

Eric Bastings

3/9/2009 04:51:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-165

John M. Ostrander, RPh, PD, PhD
Sr. Director, Regulatory Affairs
Kowa Pharmaceuticals America, Inc.
530 Industrial Park Blvd.
Montgomery, AL 36117

Dear Dr. Ostrander:

We acknowledge receipt on December 17, 2008 of your December 12, 2008 resubmission to your new drug application for diclofenac powder for oral solution.

We consider this a complete, class 2 response to our October 27, 2008 action letter. Therefore, the user fee goal date is June 17, 2009.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

2/4/2009 08:40:26 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OSE

FROM:
X_____
Eric Bastings, MD
Neurology Team Leader, Division of Neurology Products

DATE:	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 22, 2009		22-165	REMS	November 12, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
Treximet (sumatriptan and naproxen)		Migraine	

NAME OF FIRM: GSK

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS. **Risk Evaluation and Mitigation Strategy (REMS).** Clinical Team Leader is Eric Bastings 6-1039. The network location is : \\CDSESUB1\EVSPROD\NDA022165\022165.ENX

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Lana Chen, RPh, Project Manager 301-796-1056	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Eric Bastings

1/28/2009 06:38:40 PM

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 23, 2008

FROM: Eric Bastings, M.D.
Acting Deputy Director, Division of Neurology Products
HFD-120

TROUGH: Russell Katz, M.D.
Director, Division of Neurology Products
HFD-120

SUBJECT: REMS requirement for diclofenac potassium, NDA 22-165

TO: File NDA 22-165

Risk Evaluation and Mitigation Strategy (REMS) Requirements – diclofenac potassium, NDA 22-165

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of diclofenac potassium for oral solution outweigh its increased risk of cardiovascular events with the class of non-steroidal anti-inflammatory drugs, of which diclofenac potassium for oral solution is one. In reaching this determination, we considered the following:

A. It is not possible to precisely estimate the size of the population likely to use this drug. There are close to 30,000,000 migraine patients in the US, but many patients are not properly diagnosed, and therefore are not prescribed appropriate medications.
B. Migraine, in general, is not a serious or life-threatening condition, but some forms of migraine (i.e. with aura) are considered a risk factor for stroke.
C. The drug's benefit is to shorten the duration of migraine attacks, and reduce pain and symptoms associated to migraine attacks (i.e. nausea, photophobia and phonophobia).
D. Duration and frequency of therapy is variable, depending on the frequency and severity of migraine attacks in individual patients.
E. Nonsteroidal anti-inflammatory drugs, including diclofenac potassium, are associated with numerous safety risks, including an increased risk of cardiovascular events and gastrointestinal toxicity. All Nonsteroidal anti-inflammatory drugs are required to have a Medication Guide.
F. Diclofenac potassium for oral solution is not a new molecular entity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that diclofenac potassium for oral solution poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of diclofenac potassium for oral solution. FDA has determined that diclofenac potassium for oral solution is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use diclofenac potassium for oral solution.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

cc:
Orig NDA 22-165
HFD-120/RKatz/EBastings/RFarkas/LChen

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/s/

Eric Bastings
10/27/2008 02:48:06 PM
MEDICAL OFFICER

Russell Katz
10/27/2008 05:20:42 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE, Carol Holquist, RPh, Director, Division of Medication Error Prevention and Analysis (DMEPA)

FROM:
Russell Katz, M.D. Director
HFD-120/ Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10.7.08		22-165	REMS Risk Management Med Guide	June 25, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(b) (4) PRO 513 (diclofenac potassium)	High	Migraine	asap

NAME OF FIRM: ProEthic Pharma, Charlotte, NC 28281 704-831-6298

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:REMS Labeling – Med Guide review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This consult request is for review of an NSAID Med Guide. This NDA is a 505 b2 applicant. The sponsor has submitted a Med Guide with their labeling and has referenced the MG to the reference product (4 NDAs; (b) (4)) which is in the class of NSAIDS. The NSAID MG from (b) (4) is the reference MG. Pease review and comment back to us asap. Sponsor MG attached (unformatted). Please refer to NDA (b) (4) reference product). MG found in EDR under original submission dated June 25, 2007. Will contact sponsor for formatted version.

(b) (4)

[redacted]

Please call if any questions
Thanks,
Cathy 6-1123 for Lana Chen 6-1056

SIGNATURE OF REQUESTER Cathleen Michaloski, for Lana Chen R.Ph. Regulatory Project Manager 301-796-1056	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Cathleen Michaloski
10/7/2008 04:38:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM:
X_____
Eric Bastings, MD,Neurology Team Leader, DNP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Sep 25, 2008		22-165	New NDA-- Tradename Review (Cambia)	July 21, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
PRO-513 Diclofenac	Standard	Migraine	PDUFA is 10/27/08

NAME OF FIRM: ProEthic Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Available via EDR

PDUFA DATE: 10/27/08
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA
HFD- /Division File
HFD- /RPM
HFD- /Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Lana Y. Chen, Project Manager, 6-1056	☐ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

Eric Bastings

9/27/2008 05:34:31 PM

DSI CONSULT: Request for Clinical Inspections

Date: September 26, 2008

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Ronald Farcas, M.D., Medical Officer, Division of Neurology Products/HFD-120
Eric Bastings, M.D. Team Leader, Division of Neurology Products/HFD-120

From: Cathleen Michaloski, RPM, Division of Neurology Products/HFD-120

Subject: **Request for Clinical Site Inspections NDA 22-165**

Note to DSI: Clinical reviewer in DNP states that inspection of 1 site may be sufficient.

I. General Information

ProEthic Pharma., Inc.
212 South Tryon St. Suite 1280
Charlotte, NC 28221
Office phone: 704-831-6298
John Oslander, PhD. 913-342- 1288

Drug: (b) (4) Pro 513 (diclofenac potassium) powder for oral solution
Study Population: Adults
NME: No
Standard or Priority: S 505 b2 applicant

Proposed Indication: to treat acute migraine attacks with or without aura in adults.

PDUFA: 10/27/08
Action Goal Date: 10/20/08
Inspection Summary Goal Date: 10/26/08

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
#11 Michagin Head Pain Neurological Institute Attention: Joel Saper, MD 3120 Professional Drive Ann Arbor, MI O 734-677-6000 F 734 677 0227	PRO-513301	70 subjects	Migraine Acute
#19 Jerry Tomasovic, MD. Road Runner Reaserch, Ltd. 525 oak Centre Drive Suite 400 San Antonio, TX 78258 O 210-949-0505 F 210 572-0122	PRO-513301	54 subjects	Migraine Acute

III. Site Selection/Rationale

Site #11

1) High enrolling site 2) High number of subjects met no pain endpoint (12 of 20 on drug vs. 3 of 31 placebo).

Site #19

1)High enrolling site 2) High number of subjects met “no pain” endpoint ((12 of 15 vs. 3 of 21 placebo)

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
___ High treatment responders (specify):
___ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections: N/A

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Lana Chen RPM at 301-796-1056 or Ronald Farkas MD at 301-796-1931*.

Concurrence: (as needed)

_____*X*_____Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*

- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

Eric Bastings

10/2/2008 04:38:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 22-165

ProEthic Pharmaceuticals, Inc.
Attention: John M. Ostrander, PD, PhD
Sr. Director Regulatory Affairs
212 South Tryon Street, Suite 1280
Charlotte, NC 28281

Dear Dr. Ostrander:

Please refer to your June 25, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PRO-513 (diclofenac potassium) 50 mg powder for oral solution.

On May 8, 2008, we received your May 6, 2008, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 27, 2008.

If you have any questions, call James H. Reese, Ph.D., RAC, Regulatory Project Manager, for CDR Lana Chen, RPh, at (301) 796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

6/4/2008 02:48:01 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-165 **INFORMATION REQUEST LETTER**

ProEthic Pharmaceuticals, Inc.
Attention: William Maichle
Senior VP of Product Development and Technical Operations
212 South Tryon Street
Suite 1280
Charlotte, NC 28281

Dear Mr. Maichle:

Please refer to your September 28, 2007, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diclofenac potassium powder for oral solution.

We also refer to your submissions dated October 30, 2007 and March 18, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)

2. The particle size of Diclofenac Potassium drug substance is stated to be controlled by the manufacturer to NLT (b) (4) and NLT (b) (4). Provide particle size data for all drug substance lots used in manufacturing the clinical and process validation batches.
3. Please revise the acceptance limits for individual and total related impurities in the drug substance specification to NMT (b) (4) and NMT (b) (4), respectively, as per USP monograph for Diclofenac Potassium.
4. (b) (4) Mannitol were used in (b) (4) in the formulation to provide (b) (4) for the Diclofenac Potassium Powder formulation. (b) (4)
5. Provide any available data to demonstrate that storage of (b) (4) during short term (at least up to one week as stated for process validation) does not impact the quality of the product in terms of powder segregation.
6. Provide validation data for HPLC analytical method used for assay, content uniformity and dissolution with respect to method robustness.

7. Provide data to support that dissolution testing samples are adequately evaluated for linearity during validation of HPLC method.
8. Provide relative response factors for all known drug product impurities and incorporate correction factors in their calculations as necessary. Additionally, provide data for solution stability for this method.
9. Batch analyses data for additional five process validation batches were provided in the amendment submitted on 30-OCT-2007. Please clarify if these batches were manufactured with optimized operating parameters for filling and packaging of the drug product with the foil material for commercial batches and conform to child-resistant packaging as intended for marketing.
10. The primary packaging for process validation batch 007 (manufactured in April 2007) was listed as (b) (4) foil. Please clarify if it is meant to be (b) (4) foil.
11. The reference standards for Diclofenac Potassium, Impurities, A, B and C have been assigned retest dates raging from (b) (4). Please provide explanation and available supporting data to justify the assigned retest dates.
12. The description of drug product for the individual sample and outer carton are not identical (b) (4) and should be corrected.
13. The storage conditions on packet and carton label should be revised as, "Store at 25°C (77°F). Excursions permitted from 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]".
14. Please explicitly state in the How Supplied section that individual packages (Physician's Sample or Commercial) contain three co-joined single use sachets.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

4/29/2008 05:35:06 PM

MEMORANDUM OF TELECON

DATE: April 18, 2008

APPLICATION NUMBER: NDA 22-165

BETWEEN:

Name: John Ostrander, Ph.D.
Phone: PHONE 770-591-2678
Representing: ProEthic Pharmaceuticals, Inc.

AND

Name: Russell Katz, MD
Division of Neurology Products, HFD-120

SUBJECT: Statistical Analysis Plan for study **CAT458C2301**

The sponsor related that

- no SAP was submitted for study **CAT458C2301**
- The statistics used in **CAT458C2301** were similar to those of the US study.
- The same analyses used for the pain indication were used for the other three symptom endpoints.
- The results are in Table 3.2.2-2 on page 55 of the ISE and 3.2.2-3 on page 56 of the ISE.
- The results are not in the individual study reports.

FDA stated that the statistics section in the Crossover protocol is not a complete SAP.

FDA stated the following concerns:

1. Detection of carry-over effect
2. Handling of the dropouts
3. For the primary efficacy analysis, "sequence" possibly should be included in the model.
4. Whether or not a prospective SAP was created should be addressed.

FDA stated concern that appendix 5.1 is a table and not a description of data imputation as indicated.

The tcon was ended.

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/s/

James Reese
4/18/2008 01:24:11 PM
CSO

James Reese
4/18/2008 01:24:48 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

REFUSAL TO FILE

NDA 22-165

ProEthic Pharmaceuticals, Inc.
Attention: William Maichle
Senior VP of Product Development and Technical Operations
212 South Tryon Street
Suite 1280
Charlotte, NC 28281

Dear Mr. Maichle:

Please refer to your June 25, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diclofenac powder for oral solution.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Reason 1

(b) (4)

[redacted]

1 page withheld after this page as B4 (TS/CCI)

(b) (4)

Reason 2

The organization of your submission is inadequate. Regarding the nonclinical sections, the following problems have been identified:

- In Section 2.6, only the Introduction and Pharmacology Summaries provide information on diclofenac; the other summaries only state that those sections are "Not Applicable".
- (b) (4)
- (b) (4)
- The nonclinical references were only discovered through links provided in the Nonclinical Overview (see third bullet). The references themselves were not placed in the correct module, i.e., they were in Module 5 (clinical), not Module 4.

We also have identified the following issues, which are not reasons to refuse to file, but which we ask that you address:

- Please provide documentation explaining in detail the purpose of each of the SAS programs for Study CAT458C2301 and Study PRO-513301.
- For Study CAT458C2301, please provide one efficacy data set which includes all the variables needed to perform protocol specified primary and secondary efficacy analyses. For example, the following important variables are currently not in the efficacy datasets: the unique subject ID, treatment assignment, treatment sequence, etc.
- For both Study CAT458C2301 and Study PRO-513301, please include information regarding use of rescue medication at the various timepoints when efficacy data were collected in efficacy datasets.
- For Study PRO-513301, please include in the adverse events dataset the time of adverse event onset and resolution.
- For both Study CAT458C2301 and Study PRO-513301, please include in the adverse events datasets all the variables needed to perform the analyses, including treatment assignment, treatment sequence if applicable, and time elapsed between ingestion of the study medication and onset of the adverse event.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

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MEMORANDUM OF TELECONFERENCE
MEETING MINUTES

Meeting Date:	February 13, 2007
Location:	White Oak
Application:	IND 73,073
Drug:	Diclofenac
Type of Meeting:	Pre-NDA
Meeting Chair:	Russell Katz, MD, Division Director
Meeting Recorder:	Lana Chen, RPh

FDA Attendees

Division of Neurology Products
Russell Katz, MD, Division Director
Eric Bastings, MD, Neurology Team Leader
Ramesh Raman, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Kathleen Young, PhD, Pharmacology Reviewer
Ramesh Sood, PhD, Supervisory Chemist
Martha Heimann, PhD, Supervisory Chemist
Kun Jin, PhD, Statistical Team Leader
Julia Luan, PhD, Statistical Reviewer
Vaneeta Tandon, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Project Manager

Sponsor Attendees

ProEthic Attendees	**Title**
Carl Whatley	CEO
Billy Maichle	Sr. VP, Product Development & Technical Operations
John Ostrander	Senior Director, Regulatory Affairs
Kevin Swiss	Director, Technical Operations
Stuart Campbell	Director, Clinical Operations
Austin Byrne	Director, Project Management
[redacted]	Regulatory Consultant
[redacted]	Statistical Consultant
[redacted]	President of [redacted] CRO

Purpose
The Sponsor requested this Pre-NDA meeting to obtain guidance from the FDA regarding the content of their incoming NDA.

Discussion
Specific questions posed by the Sponsor were discussed:

Clinical and Statistical

1) Per the Division's comments during the October 17, 2005 Pre-IND Meeting and the Special Protocol Assessment Review, ProEthic has supplied an extensive rationale for its choice of the 50 mg dose as appropriate for the treatment of acute migraine attacks with or without aura in adults. The rationale is based on randomized clinical trial experience with Cataflam 50 and 100 mg as well as 50 mg PRO-513, the extensive marketing history of Cataflam, and relative pharmacokinetic profiles of Cataflam and PRO-513.

   Does the Division agree that the 50 mg dose is appropriate?

   FDA Response:

   FDA agrees that, based on a preliminary review, the 50 mg dose as proposed is tentatively appropriate (final decision will be based on a detailed review of the safety and efficacy findings).

   However, you must be aware that you will have to provide in the NDA evidence supporting the long term safety of your product. Because your product, especially in the fed state, appears to have a much shorter Tmax than Cataflam (i.e. 0.17h versus 0.5h for the shortest Tmax of Cataflam), you will need to make the case that the apparent faster rate of absorption of your product does not lead to a different (worse) safety profile (including long-term) than the approved product, and that the existing long-term experience with diclofenac is relevant for PRO-513. In the absence of an acceptable argument, you will need to obtain long-term safety data with your product, to meet ICH requirements (i.e. at least 300 patients treated for 6 months, and 100 patients treated for 1 year, with at least an average - per patient - of two migraine attacks treated per month). We also noted a higher rate of psychiatric events with PRO-513 than with placebo in Study PRO-513301. You will need to make the case that these AEs are not more frequent with your product than with Cataflam, and that they are not related to the shorter Tmax.

   Please also note that there are discrepancies between your text, Table 2, and Figure 1 and 2. For example, Table 2 shows a Cataflam fasting Cmax of 1160 ng/ml, but Figure 2 shows a Cmax just above 800 ng/ml. Similarly, table 2 shows a Cataflam fed Cmax of 835 ng/ml, but Figure 3 shows a Cmax around 400 ng/ml. Please provide us the corrected data.

   Meeting Discussion: Proethic clarified the discrepancies noted above.

2 [redacted] In order to comply with FDA's request for inferential analysis of the three additional outcome parameters (phonophobia, photophobia, and nausea) within our NDA, ProEthic will undertake an additional analysis using procedures consistent with those applied to our study conducted in the USA.

   Does FDA agree that, as described, such an analysis is an acceptable approach to our utilization of the available data in support of our submission?

FDA Response: Yes.

Meeting Discussion: No further discussion.

3) ProEthic intends to request a waiver for pediatric migraine studies in children under 12 years of age and a deferral until Phase IV for adolescents between 12 – 17 years of age. In accordance with the FDA's comments during the October 17, 2005 Pre-IND Meeting, ProEthic will consider a serious development plan for pediatrics and plans to discuss the pediatric program with the Division prior to implementation.

Does the Division agree that the requests for a pediatric waiver and deferral are acceptable?

FDA Response: Yes.

Meeting Discussion: No further discussion.

Chemistry, Manufacturing, and Control (CMC)

4) Is the proposed structure and format for the CMC section of this NDA acceptable to the FDA reviewers?

FDA Response:

In general, the structure and format is acceptable. You will need to submit the following drug substance information in the NDA itself.

- List of all facilities involved in manufacture and testing the bulk drug substance. This list should include complete addresses, registration numbers and contact information for each facility.
- Acceptance specification for the bulk drug substance, analytical procedures, and supporting methods validation data.
- The original Italian version of the Master Batch Record and executed batch record for the drug product should be submitted along with the English translation.

Meeting Discussion: The second point was clarified during the meeting. The drug product manufacturer's acceptance specification is needed to evaluate of the methods used to qualify the drug substance manufacturer.

5) How many paper copies, if any, will be required to be submitted in conjunction with an electronic dossier filing?

FDA Response: Submission of paper copies is not required.

Meeting Discussion: No further discussion.

6) Is the proposed method and mechanism for the submission of the flavorings elements information adequate? If not, then what method or mechanism does FDA suggest we use.

FDA Response:
Information on flavor ingredients may be submitted either directly in the NDA or by cross-reference to a supplier's DMF. Either mechanism is acceptable provided there is sufficient information to establish suitability for use.

Meeting Discussion: The Division confirmed that information submitted in the NDA should be included in Section P.4.

7) Are the numbers of samples selected and the lengths of the stability data provided adequate for the above purpose?

FDA Response:
We assume that 'numbers of samples' refers to the number of batches on stability. The proposed stability batches, and extent of stability data will be acceptable for filing the NDA. Please refer also to our response to Question 9.

Meeting Discussion: No further discussion.

8) Will the FDA agree that the stability data may be updated as a minor CMC amendment as stipulated in our comments?

FDA Response:
We generally consider a stability update to be a minor amendment. Note, however, that although additional stability data received within the first five months after NDA submission will be acceptable; data received later may not be reviewed during the same review cycle.

Meeting Discussion: No further discussion.

9) Does the FDA agree that, provided the child-resistant sachet can be successfully manufactured, the existing stability data obtained on the container-closure system may be applied to foil to obtain a suitable expiration date? Are the number of batches and number of stability time-points stipulated adequate for this expiration date assignment?

FDA Response:
In order to rely on stability data from the earlier sachet configurations, including the trial child-resistant sachet, you will need to demonstrate that the to-be-marketed sachet provides equivalent protection from moisture and air (e.g., results from permeability studies on the sealed sachet). Further, whether stability data generated using the European commercial

product will support the US commercial product will depend on the comparability of the two products with respect to drug substance source, formulation, manufacturing site, manufacturing process, etc. The expiration dating period assigned during review of the NDA will depend on the quality and extent of the stability data submitted.

Meeting Discussion: No further discussion.

Organization of the NDA

10) ProEthic intends to submit the New Drug Application in eCTD format following the ICH eCTD specification 3.2 and Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications and the regulations contained in 21 CFR 314. We will contact the FDA at esub@cder.fda.gov to inform them of our plans. We will work with the technical representative from the FDA to receive a number for a sample eCTD as well as arranging a time for a test sample.

Does the Division agree that this is acceptable?

FDA Response: Yes.

Meeting Discussion: No further discussion.

11) ProEthic plans to submit datasets for the Phase III studies in compliance with the study data specifications as found in the electronic common technical document. The datasets will be submitted in SAS transport format. The submission will include adequate documentation for the datasets including definitions, formulas for derived variables, and decodes for any classification variables so that all categories are well-defined in the documentation. We do NOT plan to submit the datasets in the CDISC format.

Does the Division agree that this is acceptable?

FDA Response:

The plan described above related to datasets submission is generally acceptable.

In addition, you need to

- include all the variables used in efficacy analysis in the efficacy data set;
- provide the derived variables and all the raw variables from which the derived variables were produced in efficacy data sets;
- provide all SAS programs by which the derived variables were produced from the raw variables and all SAS programs that produced all efficacy results; programs should be provided as both ASCII text and PDF files and should include sufficient documentation.

Meeting Discussion: ProEthic asked where the ASCII and PDF files should be located within the eCTD. The FDA confirmed that a folder under the Datasets subsection for the Statistical section would be acceptable.

12) ProEthic intends to place the Structured Product Labeling (SPL) under draft labeling in the eCTD. We will use the Guidance for Industry – *Providing Submission in Electronic Format– Content of Labeling (April 2005).*

Does the Division agree that this is acceptable?

FDA Response: Yes.

Meeting Discussion: FDA agreed to the MedDRA coding for AEs.

13) ProEthic proposes that the integrated summaries of safety and efficacy be placed in Module 5.3 of the eCTD. Is this acceptable to the Agency?

FDA Response: Yes.

Meeting Discussion: No further discussion.

14) ProEthic intends to submit only case report forms from the two Phase III trials for patients who discontinued due to an adverse event.

Does the Division agree that this is acceptable?

FDA Response: Yes.

Meeting Discussion: No further discussion.

15) ProEthic recognizes the need to establish a Post-Marketing Pharmacovigilance Program according to the regulations outlined in 21 CFR 314 and the "*Guidance for Industry, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*". It is ProEthic's feeling that routine spontaneous reporting will be sufficient for postmarketing surveillance.

Does the Division agree that this is acceptable?

FDA Response: Yes.

Meeting Discussion: No further discussion.

16) [redacted]

[redacted]

Meeting Discussion: No further discussion.

17) Are there any specific requirements for submission of the NDA that individual reviewers (pharm/tox, clinical pharmacology, medical, and CMC) in which ProEthic should be aware?

FDA Response:
No additional comments (see reviewer responses to other questions).

Meeting Discussion: No further discussion.

18) Will the Division please assign an NDA number at this time?

FDA Response:
The Sponsor may contact the Central Document Room (CDR) at 301-210-2880 to receive a pre-assigned NDA number.

Meeting Discussion: No further discussion.

Additional FDA Comments:

- You should address all our comments provided in the previous meetings, and submit these in the NDA. In addition, we request that you submit the NDA summary of Clinical Pharmacology section based on the attached Clinical Pharmacology summary format electronically with appropriate hyperlinks to the underlying data.
- You need to clarify the discrepancies between the Table 2, Figures 1 & 2 and the statements on page 13 which indicates that the Cmax for PRO-513 is significantly higher than that for

Cataflam under high fat conditions (not true according to Table 2) and that under fasted conditions, PRO-513 has an increase in Cmax of approximately 65% (not true according to Table 2) and approximately a 50% decrease in Tmax compared to Cataflam.

Additional Post Meeting Comments:

- DDMAC objects to the proposed trade name because it overstates the efficacy of the drug product. The proposed named can easily be pronounced as Therefore, the proposed tradename misleadingly implies a definitive treatment result. Without substantial evidence to support such an absolute treatment response, the proposed trade name is misleading.

  Please note that the Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

- Regarding your proposed nam, we have the following comments:
  1. DMETS does not recommend the use of the proprietary name.
  2. DMETS recommends implementation of package insert and labeling comments outlined below to minimize potential errors with the use of this product. DMETS also requests that the container labels, carton, and revised insert labeling be submitted for review as they become available.
  3. DDMAC finds the proprietary name acceptable from a promotional perspective.

[redacted]

B. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In review of the preliminary draft of the insert labeling of [redacted] DMETS has focused on safety issues relating to possible medication errors. DMETS identified the following areas of possible improvement, which might minimize potential user error.

1. General Comments

According to the draft labeling, [redacted] is described as a flavored powder packaged in cartons containing 9 unit-of-use packets. Although this product is indicated for use in the adult population, DMETS is concerned that the product could be at increased risk for accidental pediatric ingestion. There are several non-medication flavored powders available in the marketplace (e.g. Kool-Aid) that are mixed with water to form drinks that are popular with children. [redacted] also a flavored powder that is combined with water to drink, may appeal to children familiar with commercially-available powered drinks.

The comments from DMETS below include suggestions and concerns related to child-resistant packaging. We recognize that you are already evaluating child-resistant packets for the product; however, the DMETS comments provide some additional suggestions on how to minimize the potential for accidental poisoning.

DMETS notes that the insert labeling of the product advises that the product be dispensed in a "tight, [redacted] container." DMETS recommends that this wording be modified to "child-resistant container," [redacted] DMETS also recommends the sponsor consider the following recommendations to help ensure pediatric

safety as they go forward with the development of this product:

i. Avoid the use of colorful displays on the pouches that may further entice children to ingest the product.

ii. Consider packaging the product in child-resistant pouches. Child-resistant pouches have been developed for other products (such as Lidoderm, Actiq) to help minimize the potential for accidental pediatric ingestion.

iii. If the product cannot be packaged in child-resistant pouches, increase the prominence of the statement "Dispense in tight, child-resistant container (USP)" in the insert labeling, and include prominently on the outer carton of the product. In addition, on the pouch itself, a statement should advise consumers and practitioners to "Keep out of reach of children."

iv. If the product cannot be packaged in child-resistant pouches, DMETS recommends that the Sponsor consider developing a carton or container that is child resistant. This would allow pharmacists to dispense the pouches in the original container, and provide an option for patients when storing the pouches in their home. The carton or container should be functional; allowing patients to remove a pouch and close the container to protect the remaining pouches.

From a safety perspective, DMETS prefers that the pouches themselves be child-resistant since this measure has the greatest leverage in preventing accidental pediatric exposure. If only the carton is child-resistant, there is some opportunity for a pharmacist to open the carton and dispense the pouches with the child-resistant carton or container (particularly if dispensing a quantity of pouches less than the total quantity of 9). Additionally, storage of the pouches in a child-resistant container in home setting requires consumers to be vigilant; and for many reasons, this practice may not always occur.

v. If the product cannot be packaged in child-resistant pouches or a child-resistant container, DMETS recommends that the Sponsor consider the size of the individual pouches. In practice, if the product cannot be dispensed in the original container (the carton) a pharmacist will repackage the pouches into child-resistant pharmacy vials. There may also be some possibility that a pharmacist would open the pouches and dispense the powder in a smaller child-resistant container, which may not include the preparation instructions.

If the product cannot be packaged in child-resistant pouches, DMETS recommends that the pouches be of such size that the product can be repacked into a standard-size pharmacy vial (generally range in size from 6 drams to approximately 60 drams). If the pouches are too large, it could make the storage of the pouches in the vials impossible or impractical, and ultimately discourage

consumers from using a child-resistant container to store the product.

2. Package Insert Labeling

a) Clinical studies: At several points in the discussion of the clinical studies, the product is described as an immediate-release tablet. DMETS recommends that the description of the product be modified to "powder for oral solution" throughout this section and elsewhere in the labeling if necessary.

b) Under "Indications and Usage," please modify [redacted] to read "diclofenac potassium powder for oral solution". The [redacted] nature of the product is understood and need not be specified.

c) Dosage and Administration

i. DMETS questions whether 1 packet o[redacted] contains exactly 50 mg of Diclofenac. If not the insert labeling should include a weight/weight expression of the contents.

ii. DMETS is concerned that the directions for use instruct the patient to empty a packet into "approximately 50 mL of water". From a safety perspective, there are many consumers that may not be familiar with the metric system of measurement or who may not have access to tools that enable the accurate measurement of volume in milliliters. In addition, the term "approximately" is open to interpretation by both practitioners and consumers, if there is a range of volume in which the product can be mixed please be specific. DMETS also wonders what the consequences would be if the packet is mixed with a greater or lesser volume.

iii. DMETS notes a cautionary statement "Do not use liquids other than water." DMETS wonders if the effect of temperature has been studied. If so, DMETS recommends adding a statement to advise patients on the effect of temperature, or lack thereof. DMETS is concerned that patients be confused as to whether the product can be mixed with hot, cold, or room temperature water only.

iv. DMETS also notes that patients are to refill the cup with approximately 50 mL water and drink the contents again to ensure that no powder remains in the cup. If the product forms a solution as the nonproprietary name suggest (diclofenac potassium powder for oral solution), DMETS questions the necessity of this instruction. If the product does not form a

true solution in 50 mL water, DMETS recommends the nonproprietary name of the product be modified.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW AID

This is only an example of the requested review aid. This can also replace the summary section of Clinical Pharmacology and Biopharmaceutics:

- **Please fill the headings as it applies to your drug**
- **Additional specific headings can be included to suit the development of your drug/ dosage form (for e.g. For extended release products, headings like comparability of the ER to IR product, for transdermal products section on effect of application site on the PK and adhesiveness of the product etc should be included)**
- **All statements in this summary section should be annotated with links similar to your "annotated label" that would allow the reader to locate all relevant data supporting the statement. Additional links should be provided, whenever possible, for the study report and any raw data located in a SAS transport file or other format that supports the QBR statement.**
- **Within the summary section text, relevant Tables and Figures to understand the data should be included and should not be referred to some Appendix.**
- **Results from various studies, pop pk analyses should be pooled to provide information under each heading, so that consistencies across studies can be determined. If results from two similar studies are different, plausible explanations of these differences should be included.**
- **If different formulations were used during the development, the section should mention what formulation was used (to-be marketed vs. clinical service formulation)**

1.0 GENERAL ATTRIBUTES OF THE DRUG

This section contains background information about the drug and drug product to provide a context for assessing the results of the clinical pharmacology and biopharmaceutics studies.

1.1 Drug/Drug Product Information:

Dosage Form/Strengths:

Pharmacologic Class:

Chemical Name:

Physical Characteristics:

Formulation: Quantitative formula for all the dose strengths

Ingredients	Wt (mg/capsule)							
	Formulation #/Capsule Strength							
Total Size								

1.2 Proposed mechanism(s) of action and indication(s)

1.3 Proposed dosage(s) and route(s) of administration?

2.0 GENERAL CLINICAL PHARMACOLOGY

2.1 Design features of the clinical pharmacology and clinical studies used to support dosing or claims:

Here describe the type of pivotal clinical studies in brief for each indication.

For treatment of A: For e.g.

The efficacy of Drug X in patients was established in X Phase 3 randomized, double-blind, parallel, placebo-controlled multi-center trials of Y weeks duration conducted as Z treatment of patients. Of these Z studies only Y studies used the proposed dosing regimen. The X mg/day dose was not replicated in any study. Should use key studies and supportive studies that are used for labeling the product.

Short tabular descriptions may be useful here, for example:

Protocol	N	Duration	Population	X Dose
101				PER DAY AND OR BID OR TID
102				e.g.,. X MG/DAY
103				

Should repeat this information for each indication if multiple indications are proposed.

2.2. Clinical endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies

For treatment of A: For e.g.

The primary criterion to establish the efficacy of Drug X was the .....

The primary efficacy parameter was:

The secondary efficacy parameters were:

2.3 Exposure-response relationships

2.3.1 Characteristics of exposure/effectiveness relationship

For Efficacy in patients with Y:

An exposure (dose)-response analysis was conducted in Y patients pooled from X studies (Study numbers). Provide exposure or dose/response analyses data. This section should include information on all proposed doses and should also include relevant Tables and Figures of dose-response or exposure-response either from the PK-PD study conducted or from pivotal clinical trials that were used to label the drug product.

This section should also include information on any differences of exposure/dose –response for covariates such as dose, regimen, gender, age, race etc.

2.3.2 Characteristics of the exposure-response relationships for safety (dose-response, concentration-response)

If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

This section should include relevant safety information on all proposed doses and should also include relevant Tables and Figures.

This section should also include information on any differences of exposure/dose –response relationship for safety in covariates such as dose, regimen, gender, age, race etc.

e.g. Dizziness and somnolence were the most prevalent adverse events associated with treatment.

The probability for a subject to experience dizziness (AE1) increased with the dose. At the X

mg/day, the incidence of AE1 averaged to be approximately 30% (range: from >20% to <50%). Female patients apparently reported higher incidence of dizziness. It is clear that the variability was high among various trials as shown in the following figure (). The ED_{50} for incidence of dizziness was estimated to be X ± Z mg/day. ED50 for severity of somnolence was estimated to be Y ± Z mg/day.

The incidence and severity of AE1 can also be depicted by the following figures that differentiate the incidence of adverse events for the BID and TID regimens.

2.3.3 Effect on QT or QTc interval

Should include relevant Tables and figure showing Concentration-QTc relationship.

2.3.4 Justification of dose and dosing regimen based on known relationship between dose-concentration-response (In some cases, it may be possible to combine this with 2.3.2 and 2.3.3.)

The following are the sponsor proposed dosage regimen for .....patients:

Patient Population	Age Group	Starting Dose	Maximum Dose	Increments
A				
B				

Age Group:

This section should include what information is available for justifying the dose in a particular age group.

Regimen:

From a pharmacokinetic perspective:

Based on a half-life of x hours, ...appears to be suitable for the Y regimen. However, the sponsor has conducted pharmacokinetic studies to show that X mg q8h vs. Y mg q12h showed similar pharmacokinetic profiles.

Include figure where possible

Figure: Pharmacokinetics over one dosing interval

Differences in steady state plasma concentration versus time profiles for q8h and q12h dosing regimens can also be evaluated by comparing the differences in C_{maxss} and C_{minss} for these two dosing regimens. As the dosing interval is increased from q8h to q12h,

the fluctuation between Cmaxss and Cminss would be expected to increase, while Cave

would be expected to remain constant. The following figure illustrates that the differences between regimens are small when individual and mean steady-state Cmaxss, Cminss, and Cave values are compared following a dose of Y mg/day administered q8h and q12h in healthy subjects.

Include figures and Tables as necessary

From a pharmacodynamic perspective:

Include figures and Tables justifying the dose and regimen from a efficacy standpoint. Should include information on other regimens studied, but not selected for dosing recommendations and reasons why. This information can be obtained from efficacy studies, PK-PD analysis if conducted or simulation performed.

Conclusions from such analyses must be included. For e.g

These figures show that doses Y mg and above may perform better than the lowest recommended dose in patients based on the EC50 values. However, titrating with a lower dose is desirable for tolerability reasons.

These also show that both X/day and Y/day doses may be acceptable, however, for practical administration reasons X/day may be the preferred choice.

Summary efficacy Tables such as the following should be included.

Study - Summary of RRatio analysis (ITT)				
Treatment group	**N**	**Treatment differences****		**P value*****
		Mean (SE)	**95% CI**	

* Statistically significant based on Hochberg's procedure (p 0.049).
** Based on treatment means for the raw RRatio
*** Hochberg procedure applied to the ranked RRatio

Summary of secondary endpoints (ITT)							
Study	**Placebo**	**X dose and regimen**					
		BID	**BID**	**TID**	**BID**	**BID**	**TID**

*statistical significance for difference between X dose and placebo (and/or 95% CI exclude zero for Median change figures)
**subject numbers for ITT population are constant across secondary parameters in this table

From a safety perspective:

The two main adverse events of dizziness and somnolence was evaluated in terms of various doses given X/day and Y/day conditioned on severity of the adverse event. The following plots show that Y/day regimen had higher percent of observation for both dizziness and somnolence. This could be due to sustained concentration of Drug X with Y dosing.

Titration Scheme:

If a titration scheme is recommended information relevant to its selection should be included.

2.4 PK characteristics of the drug and its major metabolite?

2.4.1 Single dose and multiple dose PK pharmacokinetics?

Here Provide tables and figures on mean pharmacokinetic parameters and refer to them in the subsequent sections.

Also include in this section whether the pharmacokinetics of the drug change with chronic dose. And information on whether the multiple dose PK is predicted from single dose PK, accumulation ratio, time to reach steady state etc

2.4.2 General ADME characteristics of the drug

Absorption: may include information on transporter as well

Distribution: include information on protein binding etc

Metabolism:

Elimination:

2.4.3 Fate of drug as seen in mass balance studies

Include tables and figures from the mass balance study, also state whether these studies suggest renal or hepatic as the major route of elimination.

2.4.4 Comparison on PK between healthy subjects and patients

This section should also include information obtained from population analysis if conducted along with any definitive PK study conducted. Table and figures showing the differences in the two population should be included.

2.4.5 Degree of linearity or nonlinearity in the dose-concentration relationship

The non-linearity can be due to multiple dosing or due to increase of doses. Both should be described in this section.

This section must include Tables showing dose proportionality with statistical evaluation of the

data using power model analysis.

This section should also include figures of dose normalized PK parameters versus dose for all relevant PK parameters.

An example Table given below:

Multiple dosing Day 1 vs Day 10 —X-Y mg/day.

Table	Study - Summary Results of the Assessment of Dose Proportionality Using the Power Model Analysis			
PK Parameter	Day	AUC	β Estimate (95% CI)*	R- Estimate of the Increase in Doses Required for Doubling the AUC (95% CI)**
* ANOVA (SAS GLM Procedure)				

The results of the analysis demonstrate dose proportionality in AUC.

2.4.5 Inter-subject variability in PK parameter

Include Tables to show variability, information from different studies should be included This section should also mention the possible causes of this variability.

3.0 INTRINSIC FACTORS

In the introductory paragraph of this section highlight the key intrinsic factors that influence exposure and/response and what is the impact of such differences in efficacy and safety.

The following intrinsic factors should be discussed:

3.1 Effect of Renal Impairment:

This section should include information on the type of data available, can be presented in Tables such as....

Group Creatinine Clearance*	Renal function	N
1 > 80 mL/min	Normal	8
2 50-80 mL/min	Mildly	8
3 30-49 mL/min	Moderately impaired	8

* according to Cockcroft and Gault

Include relevant figures and Tables showing the renal clearance with change of creatinine clearance. Include 90% CI in the Tables.

Dosage Adjustment: State if needed or not, If yes then what

Dosing recommendations should be provided in Tabulate format

Sponsor's Proposal for Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total X Daily Dose[a]		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	

BID = Two divided doses; QD = Single daily dose.

[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[b] Supplementary dose is a single additional dose.

3.2 Effect of Hepatic Impairment:

information same as above should be included

3.3 Effect of age:

Elderly:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

Pediatrics:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

3.4 Effect of Gender:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

3.5 Effect of Race:

Describe the data available to draw conclusions, definitive or pop pk, number of subjects in this population. Include Tables and figures to show the differences as compared to young subjects. Also describe if any differences in efficacy or safety are observed in this population.

Dosage Adjustment: State if needed or not, If yes then what

3.6 . Effect of pregnancy or lactation:

Similar information as above, if no information available state so.

4.0 EXTRINSIC FACTORS

In the introductory paragraph of this section highlight the key extrinsic factors (such as herbal, diet, smoking, alcohol) that influence exposure and/response and what is the impact of such differences in efficacy and safety.

Also indicate in brief whether there are any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered.

4.1 In vitro basis of drug interactions

Include information on the following, this section should not be descriptive only but should

include relevant Tables to show the results and indicate which of these can lead to possible in vivo drug interactions under each of these sub headings:

Drug as substrate of CYP 450
Drug as inhibitor of CYP 450
Drug as inducer of CYP 450
Drug interaction based on protein binding
Drug as substrate of p-glycoprotein
Drug as inhibitor of p-glycoprotein
Any other transporter involved

This section can also include information from mass balance studies that suggest possible interaction, for e.g if totally renally eliminated then there is a possibility of an interaction with drugs that are also renally eliminated.

Also indicate whether the in vitro studies are conducted at relevant therapeutic concentrations (in the same units as for the plasma data (e.g. ng/ml as opposed to μM or μmole/liter)).

4.2 In vivo drug interactions

Give a tabular listing of all drugs and indicate whether a dosage adjustment is necessary. This section can be subdivided into pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic Interactions:

For e.g. Influence of Drug X on the pharmacokinetics of concomitant drugs and the influence of these drugs on the pharmacokinetics of Drug X is summarized in the following Table:

Concomitant Medication	doses evaluated	Drug X on Co-Med PK	Co-Med on Drug X PK	Evaluation Method	Dosage Adjustment

Pharmacodynamic interactions:

List any pharmacodynamic interactions observed, if any.

5.0 GENERAL BIOPHARMACEUTICS

5.1 BCS Classification of the drug

This section should include information on solubility, permeability and dissolution of the drug product, which are the basis of classifying the drug and formulation.
All relevant Tables and figures should be included.

5.2 Relative Bioavailability of the to-be marketed formulation to those used in the clinical studies

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

If the formulations are not bioequivalent this section should also indicate what safety and efficacy issues may arise, if any. In case of failed BE studies, this section should provide other supporting data regarding the to-be-marketed formulation that would aid in the decision making for the approval of the product.

5.3 Absolute Bioavailability and Relative Bioavailability to other dosage forms/route of administrations

This section should include Tables showing the test and reference comparisons, geometric mean of PK parameters, geometric mean ratios and 90% CI.

5.4 Food effect

Provide Tables as well showing the ratios and 90% CI. Also indicate if type of meal (light, medium, high) has an effect, if necessary.

Also provide the dosing recommendations based on the results of the Food Effect study. Indication if clinical trials were done with or without regard to food. If different across studies tabular listing of clinical studies and their dosing administration in relation to meals. Include any population analysis data if available.

If a fed BE study was conducted, provide justification for doing so, that will help reviewers in decision making.

5.5 Dissolution and IVIVC if appropriate

This section should include dissolution method and specifications and justification for selecting the method (for example stirring speed, media etc).

5.6 Alcohol Effect (for ER products):

This is to rule out dose dumping. Should provide the data in tabular format based on in vitro dissolution in different concentrations of alcohol. If in vivo data are available, include in this section as well.

6 .0 ANALYTICAL

This section should highlight the method used in analytical assays and provide its validation parameters. This can be done in a tabular format.

Parameter	parent	-metabolite
Method	LC/MS/MS	LC/MS/MS
LLOQ		
Linear range		
QC samples		
Inter-day accuracy and precision		
Intra-day accuracy and precision		
Freeze-thaw stability		
Benchtop Stability at RT		
Long term at –70° C		
Recovery Low Med High		

If several different analytical methods were used, the difference in method and the LLOQs should be given, for example in a Table

Analyte	Method	Assay Sensitivity ng/ml
340	LC/MS	X
344	LC/MS	Y

Assay cross validation results should also be provided.

In this section in Tabular format also provide the assay performance from each study (QC data).

Minutes Preparer: _____

Lana Chen, R.Ph.
Project Manager, DNP

Chair Concurrence: _____

Russell Katz, MD
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/s/

Russell Katz
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