CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-692 SUPPL # HFD #

Trade Name None

Generic Name tramadol HCL extended-release tablets

Applicant Name Biovail

Approval Date, If Known 9-8-05

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 questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ 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 ☒ 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 ☒ 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 ☒

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 ☒

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 ☒ NO ☐

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

NDA# 21-123 Ultracet

NDA# 21-693 Tramadol ODT

NDA# 20-281 Ultram

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 NDAs 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 ☒ 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 ☒ 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 ☒

(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 ☒

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:

BO2.CT3.021, BO2.CT3.023, and BO2.CT3.015

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 ☒
Investigation #2	YES ☐	NO ☒

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 ☒
Investigation #2	YES ☐	NO ☒

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"):

BO2.CT3.021, BO2.CT3.023, and BO2.CT3.015

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 # 59,023	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 59,023	YES ☒	! 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 ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☒

If yes, explain:

==========

Name of person completing form: Parinda Jani
Title: Chief, Project Management Staff
Date: 9-8-05

Name of Office/Division Director signing form: Bob Rappaport, M.D.
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Bob Rappaport
9/8/2005 05:43:50 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-692 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: December 31, 2003 Action Date: October 31, 2004

HFD 550 Trade and generic names/dosage form: Ralivia ER (tramadol hydrochloride extended release) 100, 200, and 300 mg tablets

Applicant: Biovail Laboratories, Inc. Therapeutic Class: synthetic opioid

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of moderate to moderately severe pain

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max X kg_____ mo._____ yr. 16 Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): deferred until after approval of adult dosage

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-692
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Carmen DeBellas
11/2/04 12:37:14 PM

RALIVIA ER (EXTENDED RELEASE) 100, 200, 300mg TABLETS

DEBARMENT CERTIFICATION

New Drug Application

Biovail Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Eugene Melnyk
President, Biovail Laboratories, Inc.

12/19/2003
Date

MEMORANDUM

To: **Nancy Clark, PharmD**
Div. of Anesthesia, Analgesia, and Rheumatology Products
HFD-170

From: **Iris Masucci, PharmD, BCPS**
DDMAC
HFD-042

Date: **August 23, 2005**

Re: **Comments on draft labeling for [redacted] (tramadol extended release) tablets**
NDA 21-692

I have reviewed the proposed label for [redacted] (March 3, 2005 version) and offer the following comments:

Pharmacodynamics

We suggest the heading "Clinical Pharmacology" appear right before the "Pharmacodynamics" subheading rather than in its current place just before "Pharmacokinetics."

Line 21

Should the first sentence here be changed to read "... is a centrally acting synthetic opioid analgesic" as in the Ultram label?

Lines 21-41

This entire Pharmacodynamics section appears to be one long paragraph. The same information is presented in the Ultram label as three paragraphs. We suggest this be broken up into multiple paragraphs for ease of reading.

Absorption

Lines 69-85

In this section, both the text and table include Latin abbreviations for drug dosing, e.g., QD and QID. Patient safety experts both within and outside FDA recommend against

using such abbreviations in labeling. "Once daily" and "four times daily" could be used instead.

Line 91, Table 2

We suggest defining "mild" and "moderate" to describe degrees of renal and hepatic impairment, e.g., adding creatinine clearance ranges and Child-Pugh classifications. Because these categories generally do not have standard definitions, adding this information will give greater context to the reader.

Clinical Studies

Lines 180-185

This paragraph presents study results using the immediate-release tramadol product. We recommend deletion of this section because the uses described here (post-op and oral surgery pain) would be "off-label" from the indications for the extended-release product.

Lines 187-208

The description of the clinical trials is confusing here. The first paragraph says that four trials were conducted but does not present results. The second paragraph describes one trial and presents results, and the third paragraph describes two trials with results. Are the trials in the second and third paragraphs among the four described initially, or are they completely different studies?

Figures 2, 3, and 4

Do the study designs and data analysis plans for these trials allow for the presentation of statistics with all these multiple timepoints for each trial?

Indications and Usage

The proposed indication is for use in "moderate to moderately severe pain." However, the description of the four studies beginning on line 187 says that the studies included patients with "chronic moderate to severe painful conditions." Should this product be approved for "moderate to moderately severe pain" or for "moderate to severe pain"? The indication should match the patient population studied.

Warnings

The entire section on "Seizure Risk" appears in bold print in the Ultram label. We suggest it be bolded here as well for consistency among tramadol products.

Information for Patients

We suggest adding an item here that patients should not take other products containing tramadol while taking this product. Such statements are often added to labels of products for which there are multiple products approved that contain the same active ingredient.

Pregnancy

We note that the pregnancy category for this product is proposed to be Category B. Why would this product be a Category B drug when Ultram is Category C? Or is the Ultram label to undergo a change? A "better" pregnancy category could be seen as a marketing advantage for this product over Ultram.

Labor and Delivery

Lines 463-471

The bulk of this section does not seem to discuss the use of tramadol in labor/delivery, but rather just provides information on its use in pregnancy in general. If this information remains in the label, we suggest it be moved to the "Pregnancy" section and the "Labor and Delivery" section be deleted if no relevant information exists.

Geriatric Use

Lines 491-492

This sentence is grammatically incorrect. A semi-colon should appear between the two independent clauses instead of a comma.

Adverse Events

This section includes exhaustive lists of adverse events that occurred in small percentages of patients. The draft guidance on the Adverse Events section of labeling discourages such lists in labeling.

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/s/

Sharon Hertz
8/29/2005 11:58:22 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories, Inc.
Attention: John Dubeck, Esquire
Agent for Biovail Laboratories
1001 G Street, N.W., Suite 500-W
Washington, D.C 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablets.

We are reviewing the Clinical section of your submission and have the following comments and information requests. Please try to complete a response as soon as possible. This information is necessary for us to complete the evaluation of your NDA.

1. Provide or point the reviewer to a listing of all Serious Adverse Events regardless of attribution to study drug.

2. Point the reviewer to a listing of all Adverse Events regardless of attribution to study drug and not already known from the Ultram® label.

3. For subjects' lab abnormalities, provide or point the reviewer to the definition of and summary analysis for outliers.

4. Provide the TRA ER exposure data in the following format to aid review.

Table x. Exposure to TRA ER in clinical studies of chronic painful conditions.

Average daily dose (mg/day)	Any length	<6 months	≥ 6 months	≥1 year
Any dose Flexible dose < 200 ≥ 200 to <300 ≥ 300 to <400 ≥ 400 placebo				

The numbers in each column are cumulative.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2516.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
10/26/04 07:16:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W.
Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride) extended release 100, 200, and 300 mg tablets.

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 within seven days for your receipt of this letter in order to continue our evaluation of your NDA.

On post-approval manufacturing batches:

- We request that one production batch of drug product for each strength be stored in largest and smallest package sizes be incorporated into the on-going stability program. These batches should be tested according to the protocol.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2516.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
10/16/04 12:53:30 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol extended release) 100, 200, and 300 mg.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response within seven days of receipt of this letter in order to continue our evaluation of your NDA.

1. Provide the analyses of patient compliance for Protocols 014 and 015.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2516.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
9/23/04 07:24:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (Tramadol hydrochloride extended release) 100, 200, and 300 mg tablets.

After a preliminary review of your proposed labeling we have the following comment. We request a prompt written response in order to continue our evaluation of your NDA.

1. Remove references specific to the ——— formulation of tramadol throughout your proposed labeling (i.e. Clinical Pharmacology and Clinical Studies sections). References to the drug substance that are not specific to a particular formulation are appropriate and should not be removed.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

Sharon H. Hertz, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Sharon Hertz
9/17/04 12:16:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol extended release) 100, 200, and 300 mg.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response within seven days of receipt of this letter in order to continue our evaluation of your NDA.

1. Please provide the demographics and clinical characteristics of patients who failed screening for Protocols 021, 023, 015 and 014 and comment on how they differ from those who entered randomization.

2. As per Table 10-1 of 015 CSR (protocol violations), six patients underwent knee reconstruction. Please clarify whether the procedure was before entering the study or during the study.

3. As per 015 CSR, analyses of treatment compliance were not performed. Given that this is a "flexible dose" study and given the known inaccuracies of patients' diaries, verify how you reliably determined the dose that patients took during this study.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2516.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Nancy Clark
9/15/04 12:12:56 PM
for Carmen DeBellas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to the teleconference meeting between representatives of your firm and FDA on September 1, 2004. The purpose of the meeting was to clarify how the *in vivo / in vitro* correlation (IVIVC) calculations in Appendix F of the NDA 21-692 submission were conducted.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page.}

Abi Adebowale, Ph.D.
Acting Team Leader, Clinical Pharmacology
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Division of Pharmaceutical Evaluation III
Center for Drug Evaluation and Research

Enclosure

FINAL

MEETING MINUTES

MEETING: Teleconference

DATE, TIME: September 1, 2004 11:00 AM

LOCATION: CDER CORP N351 Conf Room

APPLICATION: NDA 21-692

DRUG: Ralivia ER (Tramadol hydrochloride extended release) tablets

SPONSOR: Biovail

OBJECTIVE: Sponsor to provide guidance on how the calculations in the IVIVC report were conducted.

BACKGROUND:
Biovail submitted NDA 21-692 on December 31, 2003 as a 505(b)(2). The NDA was filed on February 29, 2004. The action date for this NDA is October 31, 2004. An IVIVC report was included as part of the NDA. A response to an August 3, 2004 FDA Request for Information letter concerning the IVIVC data was submitted to the Division on August 20, 2004. We requested a teleconference between FDA Clinical Pharmacologists and the Biovail Clinical Pharmacologist(s) who conducted the IVIVC calculations.

FOOD AND DRUG ADMINISTRATION (FDA) PARTICIPANTS:
Center for Drug Evaluation and Research (CDER),
Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP)

- Nancy Clark, Pharm.D. - Regulatory Health Project Manager
- Patrick Marroum, Ph.D.- Clinical Pharmacologist, Team Leader OCDP (DPE1)
- Lei Zhang, Ph.D. – Clinical Pharmacologist, Division of Pharmaceutical Evaluation III (DPEIII)

SPONSOR PARTICIPANTS:
Biovail

- John F Weet, Ph.D.,VP Regulatory Affairs
- Okpo Eradiri, Ph.D., Sr. Director, Toxicology and Pharmacokinetics
- Gene Wright, Pharm.D., Ph.D., VP, Project Management & Pharmacokinetics
- Jacqueline Little, M.Sc., Director, Regulatory Liaison
- Amanda Gibson, Ph.D., Product Manager
- Iris Calle, Regulatory Affairs Assistant

Meeting Summary:

- Dr. Marroum did not agree with the Level A in-vitro/in-vivo correlation that was obtained for Ralivia ER Tablets. Specifically, the Division did not accept the computational approach used to correct for differences in bioavailability which are related to differences in release rate. Since one correction factor applicable to all possible release rates did not emanate from the model, Dr. Marroum stated that the Division would not accept the 1:1 correlation established in the report.
- Dr. Marroum recommended that Biovail should re-do the computations using the method of Gillespie (1997) to correct for differences between in-vitro and in-vivo release profiles.
- Dr. Marroum asked Biovail to make an effort to submit this recalculation to the NDA by the end of September, 2004, for IVIVC results to be used in setting dissolution specifications for Ralivia ER. He reiterated that IVIVC *per se* is not relevant for approvability of the NDA.
- If not available by end of September, dissolution specifications for Ralivia ER will be set independent of the IVIVC results. However, Biovail can submit the new calculations after the PDUFA date and if the Division deems the new computations to be acceptable and a 1:1 correlation is established, the specifications will be revised accordingly.
- The Division agreed that while deconvolution based on individual data is preferable, computations based on mean data will be acceptable since Biovail has demonstrated in the initial response that the two procedures give similar results.

All pages are accounted for in this document.
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/s/

Abi Adebowale
9/15/04 03:19:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (Tramadol hydrochloride extended release) 100, 200, 300 mg tablets.

We are reviewing your submission and have the below information requests. We request a prompt written response within seven days of your receipt of this letter in order to continue our evaluation of your NDA.

Chemistry

- Verify the following: [redacted] the manufacturing site [redacted], called the Office of Compliance stating that the API is being transferred to another site.
    - The Office of Compliance and our Division need this information in writing.
    - [redacted] needs to be cancelled from the application or withdrawn. Otherwise, the Office of Compliance will Withhold, or reject it, based upon Firm Not Ready.

Clinical

- Direct our reviewer to the Financial Disclosure form 3455 and the list of investigators who received significant payments of other sorts.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
9/9/04 04:35:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablets 100, 200, 300 mg.

We are reviewing the Clinical section of your submission and have the following information request. We request a prompt written response, within seven days of receipt of this letter, in order to continue our evaluation of your NDA.

- Please provide or direct the reviewer to the number of patients screened and reasons for not entering Studies 021, 023, 015, and 014.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
9/2/04 11:21:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride) 100, 200, 300, ——— mg extended release tablets.

We are reviewing the Clinical and Statistical sections of your submission and have the below information request. We request a prompt written response within seven days of your receipt of this letter in order to continue our evaluation of your NDA.

Protocol 015 in Osteoarthritis:

Provide an SAS dataset with baseline pain intensity scores for all randomized patients who received at least one dose of study medication (124 and 118 patients for Tramadol ER and placebo, respectively).

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
8/25/04 03:55:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman LLP
1001 G Street, N.W, Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride) extended release tablets.

We are reviewing the Clinical Pharmacology (Biopharmaceutical) and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response within one week of your receipt of this letter in order to continue our evaluation of your NDA.

Clinical Pharmacology

An error appears in the calculation of time to maximum values (Tmax) in the Ultram® tablets every 6 hours (Q6h) treatment arm in Study Report # 2551 (B01-567PK-TRAP03). For example, from the mean plasma concentration time profile, Tmax for tramadol is around 22 hours, not 2 hours after single-day dosing (Q6h) of Ultram®. Please recalculate the Tmax values for tramadol and M1 that properly reflect the time to the occurrence of Cmax for all treatment arms in Study Report # 2551 (B01-567PK-TRAP03).

Chemistry- List of Deficiencies

1. The following comments pertain to the Drug Substance:
   - DMF —— submitted —— has been reviewed and found deficient. The DMF holder has been notified of the deficiencies. A satisfactory review of the DMF is necessary before the NDA can be approved.
2. The following comments pertain to the Drug Product:
   - The drug product specification is insufficient since it contains only a single HPLC identification test (see ICH Guidance Q6A). Please provide at least one additional ID test to assure the identification of the drug product.

3. The following comments pertain to the Drug Substance and the Drug Product:

- Acceptance criteria for residue solvents should be established based on manufacturing capability. Please provide the data to support your proposed limits on residual solvents present in the drug substance and the drug product.
- The acceptance criteria for the [redacted] was NMT [redacted]. Please explain the difference.

The dissolution acceptance criteria for release were stated to be:

Hours	Dissolution
2 hours:	
4 hours:	
8 hours:	[redacted]
16 hours:	

The dissolution acceptance criteria for stability were stated to be:

Hours	Dissolution
2 hours:	
4 hours:	[redacted]
8 hours:	
16 hours:	

Do the dissolution criteria for release differ with the dissolution criteria for stability? Please explain.

4. Please submit additional stability data for the drug product packaged in foil or foil blister containers.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
8/10/04 01:02:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories, Incorporated
Attention: John B. Dubeck
Keller and Heckman LLP
1001 G Street N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablets.

We are reviewing the Clinical Pharmacology (Biopharmaceutics) section of your submission and have the below comments and information requests. We request a prompt written response within one week of receipt of this letter in order to continue our evaluation of your NDA.

1. Submit all data files (including raw *in vitro* release data) and control files (for deconvolution and convolution) electronically in order to facilitate our validation of the analysis.

2. Calculate the individual fraction of drug absorbed relative to individual immediate release (IR) value for each subject. Using this data you should then calculate a mean relative fraction of drug absorbed, which would be correlated to the mean amount of drug dissolved *in vitro*. No scaling factor is needed in this case because IR is used as the reference and all the values are normalized to the IR values.

3. The scaling factor used in the Report 2003-14 is not acceptable for *In Vitro-In Vivo* Correlation (IVIVC) analysis. If a scaling factor is needed, the scaling factor should be the same for all the formulations. Clarify how you back-scaled the results for the prediction of the plasma concentrations.

4. Clarify why the data from the fast formulation was excluded. The IVIVC results provided seem to meet the internal predictability even with the fast formulation included.

5. The conclusion from IVIVC analysis will affect the dissolution specifications. If IVIVC is not established, the dissolution specifications will need to be based upon the observed product performance.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Nancy Clark
8/3/04 10:53:56 AM
For Carmen DeBellas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories, Incorporated
Attention: John B. Dubeck
Keller and Heckman LLP
1001 G Street N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablets.

We are reviewing the Clinical section of your submission and have the below comments and information requests. We request a prompt written response within one week of receipt of this letter in order to continue our evaluation of your NDA.

Protocol study 015 in Osteoarthritis:

1. Provide analyses of all adverse events, serious adverse events, and discontinuations due to adverse events by body system and by patient's final Tramadol ER dose.

2. Present us with efficacy analyses by Tramadol ER dose at the time of the efficacy evaluations (Pain VAS, WOMAC Pain, WOMAC Function and Patient Global assessment). Additionally, provide landmark analyses at week 12 and average analyses over the entire treatment period.

3. Please present the analyses of concomitant analgesic medications used during study 015 in osteoarthritis.

4. In an effort to aid our review, please direct us to the folder name and page that list the patients' laboratory measurements.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories, Incorporated
Attention: John B. Dubeck, Esq.
Keller and Heckman LLP
1001 G Street, N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA 21-692) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablets.

We are reviewing the Statistical section of your submission and have the below comment and information request. We request a prompt written response within one week of receipt of this letter in order to continue our evaluation of your NDA.

- Data for the sensitivity analyses for studies 014, 015, 021, and 023 is incomplete. Please send us the full descriptions for variables and variable values of the efficacy data.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
7/30/04 11:55:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories, Incorporated
Attention: John B. Dubeck
Keller and Heckman LLP
1001 G Street N.W., Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablets.

We are reviewing the Clinical section of your submission and have the below comments and information requests. We request a prompt written response within one week of receipt of this letter in order to continue our evaluation of your NDA.

1. Protocol 015- low back pain
    a. Provide a table for serious adverse events in the run-in period and a separate table serious adverse events during the double blind period of study 015, by organ system and by tramadol dose at the time of onset of the adverse event.

    b. Secondly, provide a table for discontinuations due to adverse events, regardless of seriousness, during the run-in period and a separate table of discontinuations during the double-blind period of study 015 (regardless of when patients started) by organ system and by tramadol dose at the time of discontinuation.

    c. Table 14,3.2.4.2 of serious adverse events during entire study period, all entered patients:
        i. patient 060 had a tonic clonic seizure
        ii. patient 022 had chest pain and CHF
        iii. patient 010 had chest pain/epigastric pain

        All three patients are listed as "entered" but "not randomized". Please clarify at what time during the study they had the serious adverse event and the dose of tramadol at the time of the event.

    d. For patients who completed the run-in period and were randomized to placebo: Provide a patient list of adverse events, regardless of severity, and if and when the patient discontinued placebo.

e. Lastly, please provide Case Report forms of all patients who requested withdrawal from study 015.

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
7/28/04 06:13:37 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck
US Agent
Keller and Heckman LLP
1001 G Street, N.W, Suite 500-West
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) tablet 100 mg, 200 mg, and 300 mg.

We are reviewing the Clinical 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.

- Please provide the number of patients remaining at each time point analyzed in each treatment group in each of the four studies submitted.

- Please clarify Table 11-3, page 52 of protocol B00.CT3.014.TRA P03 CSR. In particular, the right side of the table, which contains four columns: Treatment, 300 mg, 200 mg, and 300 mg again. What does Treatment refer to and why are there two columns for the 300 mg dose?

If you have any questions, call Nancy Clark, PharmD, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
7/20/04 03:10:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 59,023
IND 66,859

Biovail Laboratories Incorporated
Attention: John B. Dubeck
Esquire
Keller and Heckman LLP
1001 G Street, N.W.
Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to the fax from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Product on October 10, 2003 containing the draft responses to the questions submitted for the preNDA meetings for IND 59,023 SN 049 August 19, 2003 SN 049, additional information submitted September 22, 2003 SN 052 and PIND 66,859 SN 002. Per the Sponsor's October 13, 2003 voice mail request the October 14, 2003 face-to-face meeting was cancelled. The Sponsor was advised that the draft responses provided on October 10, 2003 would be finalized within 30 days and recorded as the minutes.

The official finalized responses to the questions provide in the above mentioned submissions are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the finalized responses.

If you have any questions, call Barbara Gould, Project Manager, at 301 827-2090.

Sincerely,

{See appended electronic signature page}

Lee. S. Simon, M.D.
Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

17 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

10 § 552(b)(5) Deliberative Process

*Withheld Track Number: Administrative-*_____

MEETING MINUTES

MEETING DATE: February 12, 2002 **TIME:** 3:30 P.M. **LOCATION:** Corp S300

IND 59,023 **Meeting Request Submission Date:** November 26, 2001
Briefing Document Submission Date: January 14, 2001

DRUG: tramadol hydrochloride extended-release tablets, 100 mg

SPONSOR/APPLICANT: Biovail Laboratories Incorporated

TYPE of MEETING: Guidance Meeting

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics & Ophthalmic Drug Product**
Jonca C. Bull, M.D.	Deputy Director, Acting Director Office of Drug Evaluation V
Lee S. Simon, M.D.	Division Director
Lawrence Goldkind, M.D.	Deputy Division Director
James Witter, M.D., Ph.D.	Acting Medical Team Leader
Lourdes Villalba, M.D.	Medical Reviewer
Joel Schiffenbauer, M.D.	Medical Reviewer
Dennis Bashaw, PharmD.	Biopharmaceutics Team Leader
Suktae Choi, Ph.D.	Statistical Reviewer
Barbara Gould	Project Manager

INDUSTRY PARTICIPANTS:	**Biovail Laboratories Incorporated**
Dr. Paul Desjardins	VP – Product Development Operations
Dr. Kenneth Albert	VP – Clinical Development
Dr. Theo Gana	Director – Clinical Research
Dr. Okpo Eradiri	Senior Director – Pharmacokinetics & Toxicology
Mr. Wayne Kreppner	Manager – Regulatory Affairs

MEETING OBJECTIVES:

1. Review the Phase III osteoarthritis (Study No. B00.CT3.014.TRA P03) and low back pain (Study No. B00.CT3.015.TRA P03) study results
2. Obtain Agency concurrence on the design of the Phase III clinical program.
3. Obtain Agency concurrence on the proposed NDA filing strategy and indication

BACKGROUND INFORMATION:

Biovail intends to file ( ) New Drug Application for tramadol hydrochloride extended-release tablets 100 mg for the following indications:

- Management of moderate to moderately severe pain

QUESTIONS for DISCUSSION with FDA RESPONSE:

1. **Does the Agency agree that the proposed clinical program will support the proposed indications?**

   FDA Response:
   No.

   a) [redacted]

   b) Management of moderate to moderately severe pain is no longer an indication. For the last several years the scientific community and the Division's approach have evolved into separating acute from chronic pain. Your package does not contain acute pain studies, therefore it appears that you are pursuing the chronic pain indication.

   The current best guidance for development of an analgesic for a chronic pain indication is replication of evidence in well-controlled trials of 12 weeks duration in at least three different models of chronic pain. Primary endpoints include measures of pain, function and patient global assessment. Please include SF-36 in all chronic pain studies.

   The two completed studies in chronic pain (one in OA and one in chronic lower back pain--LBP) are not considered adequate pivotal studies. The OA study used a flexible dose regimen. Flexible dose studies do not allow adequate evaluation of the minimal effect dose or dose-response in terms of safety or efficacy. The LBP study had a 3-week run-in period. Patients enrolled in studies with open label run-in periods are considered a selected sub-population of tramadol-tolerant patients whose safety profile does not extrapolate to the general population.

   c) Safety database:
   - Patients ultimately enrolled in studies with open-label run-in periods are considered a selected sub-population of tramadol-tolerant and responsive patients whose safety profile does not extrapolate to the general population.
   - Safety profile of tramadol ER in the elderly should be addressed.
   - Potential for abuse of tramadol ER should be addressed.

2. **Does the Agency have any comment on the proposed dose-titration strategy for the remaining osteoarthritis and low back pain studies and our overall approach to addressing the dose-titration requirement for this product?**

FDA Response:
Please clarify the question. Also clarify what tablet form will be used for the 300 mg dose (100 mg x3 or 300 mg x1). The Agency does not have a "requirement for dose titration". The dose titration schedules you propose appear adequate from the safety point of view, however:

a. Run-in periods that exclude intolerant subjects from the efficacy assessment of a trial are problematic for multiple reasons including:
   1. lack of generalizability to the intended population
   2. inability to adequately assess risk:benefit

b. Titration periods in a clinical trial will profoundly inform a label for safe and effective use of the drug. If an efficacy study is performed in such a way that efficacy is only established after multiple doses, such information will be required in the label and information on safety of concomitant therapy that will allow for pain management during slow titration of the proposed product will be needed.

c. Clear delineation of a minimum effective dose is necessary for labeling of a drug product. Your studies suggest that tramadol E.R. 200 mg dose is not as effective as the 300 mg dose. Inclusion of the 200 mg dose in the label requires adequate evidence of efficacy at that dose.

3. **Does the Agency have any comments regarding our operational definitions for the two ITT populations?**

FDA Response:
Intent-to-treat population of safety and efficacy should be identical. For the definition of ITT Efficacy Population, "and had at least one post-baseline efficacy assessment." should be deleted.

4. **Will the agency concur with our request for a pediatric waiver?**

FDA Response:
No. You may request a deferral of pediatric studies.

5. **Does the Agency agree that the proposed healthy volunteer pharmacokinetic studies, special population pharmacokinetic studies and the drug interaction study will be sufficient to support the Tramadol ER tablets new drug application?**

FDA Response:
In general the trials seem adequate, however, without a chance to review the specific protocols in question we are unable to definitively comment on their design and/or methodology.

6. Does the Agency agree with the proposed strategy for Tramadol analytes and enantiomers?

FDA Response:
No, while we generally agree with the proposal we are concerned that the hepatic insufficiency trial is going to use an achiral assay. Given the concerns with tramadol and the potential for altered disposition in this patient population we would recommend that the specific chiral assay also be applied to this study.

ADDITIONAL SALIENT POINTS

❖

- ❖ Phase III studies conducted with Tramadol ER were flexible dose studies. Therefore the OA study completed by the Sponsor is not considered to be a pivotal study. The studies may be considered as supportive studies in the NDA.
- ❖ The Sponsor was informed of the Division's current thinking regarding an overall chronic pain indication, which would require replicate studies in 3 different models of chronic pain.
- ❖ Examples of models to be considered are cancer pain, osteoarthritis and fibromyalgia.
- ❖ Titration as performed in the pivotal trial would need to be included in the label, since the Division expects patients to be taking concomitant medications..

Additional FDA Comments:

Financial Disclosure:

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety. Please refer to "Financial Disclosure by Clinical Investigators" Final Rule February 2, 1998.

Pediatric Rule:

Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA (or sNDA).

Pediatric Exclusivity: (Note that choosing to pursue Pediatric Exclusivity is optional for a sponsor and not required.)

Under the Food and Drug Administration Modernization Act, an approved application may have the opportunity for an exclusivity extension based on the completion of pediatric studies. If you choose to pursue pediatric exclusivity, your plans for pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPRS) should be submitted so that we can consider issuing a Written

Request. For complete information, please refer to the FDA/CDER web page, http://www.fda.gov/cder/guidance/index.htm. "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Drug and Cosmetic Act".

ACTION ITEMS:

1. The sponsor will provide protocol for special protocol assessment.
2. Project manager will convey minutes within 30 days.

Barbara Gould Date
Project Manager

Concurrence Chair:

Lee S. Simon, M.D. Date
Division Director

Initialed by: DBashaw/*26 June 2002 no changes*
LVillalba/*03 July 2002, 09 July 2002 w/changes*
JWitter/*05 July 2002 w/changes*
LGoldkind/*05 July 2002 w/changes*

MEETING MINUTES

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/s/

Lee Simon
7/11/02 04:56:49 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Biovail Laboratories Incorporated
Chelston Park, Building 1, Ground Floor
Collymore Rock, St. Michael
Barbados, West Indies

2. TELEPHONE NUMBER *(Include Area Code)*
(202) 434-4125

3. PRODUCT NAME
Tramadol Hydrochloride ER

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-692

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

Ultram NDA 20-281
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4676

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
	Vice President, Regulatory Affairs	10/29/03

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-692	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: Ralivia ER (tramadol hydrochloride extended release) 100, 200, and 300 mg tablets		Applicant: Biovail Laboratories, Inc.	
RPM: Nancy Clark, PharmD.		HFD-550	Phone # 301-827-2516

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (X) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 20-281 Ultram

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	N/A
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 31, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4676
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• 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 **N/A** 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).	**N/A**
• [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 box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) (X) 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? (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)? *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 box below (Exclusivity).* *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?	(X) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)? *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 box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the 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 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 box below (Exclusivity).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	(X) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • 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.)	N/A
• Is there existing orphan drug exclusivity protection for the "same drug" 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.*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	September 24, 2004
• Original applicant-proposed labeling	December 31, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC- October 6, 2004 DMETS- pending as of 11/2/04 DSRCS- February 26, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	February 12, 2002
• Pre-NDA meeting (indicate date)	October 14, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other (IVIVC clinical pharmacology meeting)	September 1, 2004
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Division Director- October 29, 2004 Deputy Director- October 26, 2004 Team Leader- October 28, 2004
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	October 29, 2004 for 4 reviews
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	In Clinical review October 29, 2004
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	October 18, 2004
❖ Biopharmaceutical review(s) *(indicate date for each review)*	October 19, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	October 1, 2004
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	October 18, 2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	October 18, 2004
• Review & FONSI *(indicate date of review)*	October 18, 2004
• Review & Environmental Impact Statement *(indicate date of each review)*	October 18, 2004
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	October 20, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	October 6, 2004

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) 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.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Carmen DeBellas
11/2/04 03:21:26 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated
Attention: John B. Dubeck
US Agent
Keller and Heckman LLP
1001 G Street, N.W, Suite 500-W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) 100 mg, 200 mg, and 300 mg tablets.

We also refer to your submission of Study 2677 included with the NDA application.

We are reviewing the Clinical Pharmacology (Biopharmaceutical) 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.

- Study 2677, an In Vitro/ In Vivo Correlation (IVIVC) study report is included in this NDA. We do not find a conclusion about what type of correlation was obtained, Level A or Level C. It is your responsibility to indicate how this information is to be used as part of the NDA application.
- Please refer to the "Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations" for in vitro/in vivo correlation analysis and its application to the drug approval process (http://www.fda.gov/cder/guidance/index.htm). This information should be submitted as soon as possible otherwise review of the in vitro/in vivo correlation data will be deferred until such time as a complete report is available.

If you have any questions, call Nancy Clark, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
7/8/04 03:44:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

Biovail Laboratories, Incorporated
Attention: John B. Dubeck
U.S. Agent
Keller and Heckman, LLP
1001 G Street, N.W. Suite 500 West
Washington, D.C. 20001

Dear Mr. Dubeck:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ralivia ER (tramadol hydrochloride ER) Tablet 100 mg, 200 mg, and 300 mg
Review Priority Classification:	Standard (S)
Date of Application:	December 31, 2003
Date of Receipt:	December 31, 2003
Our Reference Number:	NDA 21-692

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 29, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 31, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
5600 Fishers Lane
Rockville, MD 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room, N115
9201 Corporate Boulevard
Rockville, MD 20850

If you have any questions, call Stacey N. Welch, Regulatory Health Project Manager, at 301-827-2516.

Sincerely,

{See appended electronic signature page.}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Stacey Welch
4/1/04 12:34:00 PM
for Carmen DeBellas, R.Ph.

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

FILING COMMUNICATION

NDA 21-692

Biovail Laboratories, Incorporated
Attention: John B. Dubeck
U.S. Agent
Keller and Heckman, LLP
1001 G Street, N.W. Suite 500 West
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your December 31, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride ER) Tablet 100 mg, 200 mg, and 300 mg.

We also refer to your submission dated February 25, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 29, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential clinical review issues:

1. This submission lacks acute pain studies and so would not support the same indication as the referenced approved product.

2. An indication "for the treatment of chronic moderate to moderately severe pain" may be entertained; however, preliminary review of the submission suggests that the chronic efficacy studies included in the application may:

   A. be inadequate in design to be considered pivotal studies (B00.CT3.015.TRA.P03 and B00.CT3.014.TRA.P03) as previously noted by us in an Advice Letter dated February 21, 2001, and during the End of Phase 2/Guidance Meeting of February 12, 2002, or

   B. have failed the pre-specified primary efficacy analyses proposed in the original protocols (B02.CT3.021.TRA.P03 and B02.CT3.023.TRA.P03).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Stacey N. Welch, Regulatory Health Project Manager, at 301-827-2496.

Sincerely,

{See appended electronic signature page.}

Brian E. Harvey, M.D., Ph.D.
Acting Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Brian Harvey
3/12/04 02:58:33 PM