CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-693

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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
21-693

NAME OF APPLICANT / NDA HOLDER
Biovail Laboratories, 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)
Ralivia FlashDose (tramadol hydrochloride orally disintegrating tablets)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Tramadol HCl	50 mg

DOSAGE FORM
solid, oral

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

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	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.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

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.)*	

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
John B. Dubeck	2/17/04

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 John B. Dubeck, Esq.	
Address Keller and Heckman LLP 1001 G Street, N.W. Suite 500-W	City/State Washington, DC
ZIP Code 20001	Telephone Number (202) 434-4125
FAX Number *(if available)* (202) 434-4646	E-Mail Address *(if available)* dubeck@khlaw.com

EXCLUSIVITY SUMMARY FOR NDA # _21-693_____ SUPPL #_____

Trade Name _____ Generic_tramadol_____

Applicant'sName__Biovail_Technologies____HFD 550_____

Approval Date If Known: January 11, 2005__AE
May 8, 2005 AP

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 /___/ NO /x___/

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.

_The Applicant's letter states that __the formulation would deliver an equivalent amount of drug to the systemic circulation as the listed drug Ultram._____

_____

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 /_x__/

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

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 Writen 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. **NA**

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# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product. **NA**

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

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:

_____

_____

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"):

_____ _____

_____ _____

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 /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ 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 /___/ 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 /___/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-693 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: April 1, 2004 Action Date: January 11, 2005 Resubmission Action Date: May 8, 2005

HFD 550 Trade and generic names/dosage form: Ralivia (tramadol) Flashdose

Applicant: Biovail Technologies, Ltd. Therapeutic Class: 3S

Indication(s) previously approved: New Approval

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

Number of indications for this application(s): 1

Indication #1: Management of moderate to moderately severe pain in adults

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

Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred X____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

:omplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ 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): 05/08/09

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 21-693
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)

RALIVIA™ FlashDose® (orally disintegrating) 50 mg 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.

March 5, 2004
Date

OVERNIGHT COURIER

May 5, 2005

Brian Harvey, MD, Acting Director
Division of Anti-inflammatory, Analgesic
And Ophthalmologic Drug Products
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA #21-693
Tramadol Hydrochloride Orally Disintegrating Tablets
Amendment: Response to FDA Request for Carton and Blister Pack Label Revision

Dear Dr. Harvey:

Reference is made to NDA #21-693 submitted to the Division on March 11, 2004 and filed on May 11, 2004, the Division Approvable Letter of January 11, 2005, and the Complete Response to the Division's Approvable letter submitted March 8, 2005.

The purpose of this submission is to provide Biovail's agreement to the Division's and DMETS' proposed revision to the carton and blister pack labeling as specified in a telephone conference on May 4, 2005, as follows:

Tradename

(Tramadol HCl Orally Disintegrating Tablets)

50 mg

(equivalent to 50 mg tramadol)

Our client Biovail Laboratories International SRL has requested that we provide this information. Should you have any questions, please do not hesitate to contact Jacqueline Little at (908) 927 – 1753.

Sincerely yours,

John F. Weet, Ph.D.
Vice President
Regulatory Affairs
Biovail Technologies Ltd.

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908.927.1748
F 908.927.1749
jack.weet@biovail.com

From: Reedy, Kathleen R
Sent: Wednesday, May 04, 2005 4:40 PM
To: Little, Jacqueline
Subject: Final adjustment to the blister unit dose label

DMETS' first preference is for the product strength to be expressed as presented below, since it is consistent with USP nomenclature of salts. In addition, it allows for an increased prominence of the product strength as compared with the other two presentations listed in our April 26, 2005 labeling review (See ODS Consult 04-0171-1).

Tradename
(Tramadol Orally Disintegrating Tablets)
50 mg

However, if you would still like to continue to express the product strength as presented in the 5/4/05 labeling, DMETs suggests increasing the prominence of the product strength by also presenting it outside of the equivalency statement. For example:

Tradename
(Tramadol Orally Disintegrating Tablets)
50 mg
(equivalent to 50 mg tramadol)

Kathleen R. Reedy, MS, RDH
Regulatory Health Project Manager
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
301 827 2533 Fax: 301 827 2531
Room N339, 9201 Corporate Boulevard, Rockville, MD 20850
reedyk@cder.fda.gov

Reedy, Kathleen R

From: Jacqueline Little [Jacqueline.Little@biovail.com]
Sent: Tuesday, May 03, 2005 6:45 PM
To: Kathleen Reedy (E-mail); arnwinek@cder.fda.gov
Cc: Jack Weet
Subject: NDA 21-693 carton and blister packaging

Importance: High



Tramadol ODT Tramadol ODT tramadol ODT
ıg Carton_3May)mg Blister Packlister label-Apr..

<<Tramadol ODT 50mg Carton_3May2005.pdf>> <<Tramadol ODT 50mg Blister Pack_3May2005.pdf>> <<tramadol ODT blister label-April 14.pdf>>

Dear Kathleen,

Please find attached newly revised versions of the carton and an individual unit blister in accordance with the Division letter dated April 28, 2005. For version control I have placed today's date on the page for each.

The carton now displays the dosage wording that Dr. Hertz recommended.

For reference, I attached the 6-blister configuration I emailed you on April 14. I regret that I was unable to recreate a new 6-blister display because I do not have the software to do so. Please view the individual unit above as reproduced for all 6 units of a blister pack.

> Best regards,
>
> Jacqueline
>
> Jacqueline Little, M.Sc.
> Director, Regulatory Liaison
> CNS & Pain
> Biovail Technologies, Ltd.
> 700 Routes 202/206 North
> Bridgewater, NJ 08807
> Tel 908-927-1753
> Mobile 908-216-1190
> Fax 908-927-1553
> e-mail: Jacqueline.Little@biovail.com
>

3 Page(s) Withheld

_____ Trade Secret / Confidential

✔ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-1

OVERNIGHT COURIER

April 29, 2005

Brian Harvey, MD, Acting Director
Division of Anti-inflammatory, Analgesic
And Ophthalmologic Drug Products
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA #21-693
Tramadol Hydrochloride Orally Disintegrating Tablets
Amendment: Revised Tradename, Blister Pack, and Carton Label

Dear Dr. Harvey:

Reference is made to NDA #21-693 submitted to the Division on March 11, 2004 and filed on May 11, 2004, to the Approvable Letter of January 11, 2005, and the proposed tradename submission of April 26, 2005.

With reference to a discussion with Nancy Clark on April 29, 2005, Biovail has decided to defer the formal nomenclature of Ultram® ODT. In view of this decision, we ask that the proprietary name for tramadol be hereby submitted as:

TRADENAME ® ODT (tramadol hydrochloride orally disintegrating tablets)

Please see the enclosed carton and blister pack labeling that has been revised accordingly.

Our client Biovail Laboratories International SRL has requested that we provide this information. Should you have any questions, please do not hesitate to contact Jacqueline Little at (908) 927 – 1753.

Sincerely yours,

John F. Weet, Ph.D.
Vice President
Regulatory Affairs
Biovail Technologies Ltd.

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908.927.1748
F 908.927.1749
jack.woot@biovail.com

OVERNIGHT COURIER

April 28, 2005

Brian Harvey, MD, Acting Director
Division of Anti-inflammatory, Analgesic
And Ophthalmologic Drug Products
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA #21-693
Tramadol Hydrochloride Orally Disintegrating Tablets
Amendment: Revised Blister Pack and Carton Labels

Dear Dr. Harvey:

Reference is made to NDA #21-693 submitted to the Division on March 11, 2004 and filed on May 11, 2004, and to the Approvable Letter of January 11, 2005, along with the fax received on April 28, 2005 from Carmen DeBellas requesting changes to the blister label and carton labeling. The purpose of this submission is to provide the revised blister label and carton labeling.

Item A.1.a. – Unit Dose Peel-Off Label (Front)

We note the strength is based on the active moiety and not the hydrochloride salt. Thus, the expression of strength should be revised in one of the following manners to reflect this. (Please note that DMETS prefers choice "i" as this is consistent with USP nomenclature of salts.)

We agree with the Division's choice of expression of strength. The language in the attached unit dose label is consistent with Item i, in your letter. The name Ralivia is hereby replaced by the name "ULTRAM ODT", consistent with our amendment of April 26, 2005.

Ultram® ODT
(Tramadol Orally Disintegrating Tablets)
50mg

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

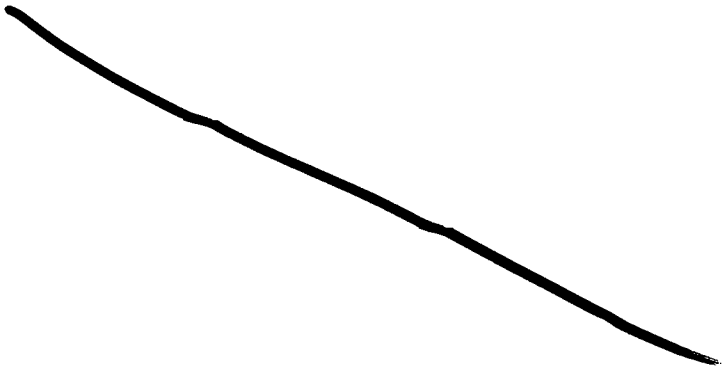
T 908.927.1748
F 908.927.1749
jack.weet@biovail.com

Item A.1.b.

Increase the prominence of the established name so that it appears at least one-half the size of the proprietary name.

We agree with the Division's recommendation, and are including artwork to reflect 18 point type for the proprietary name and 12 point type for the established name. Please note that 9 point type would be 50% of the font size of the proprietary name. To be conservative, we are including type that exceeds the minimum requirement by 50%.

Item 1.A.c.



Item A.2.a. – Blister Label (Back)

Bold the statement "Do not push tablet through".

For the purposes of this submission, we would propose that the statement "Do Not Push Tablet Through" be bolded, but included in the text on the unit dose front, with the rest of the pertinent product information, as shown in the attached artwork for the unit dose blister card. This would be included as a separate bullet point line.

Item B.1. – Carton Labeling

See comments A-1, A-2 and A-3.

Changes have been introduced into the draft label to reflect the revisions requested in A-1 and A-2.

Please note that there is not an A-3 in the letter for reference.

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908 927.1718
F 908 927.1749
jack.weet@biovail.com

Item B.2.

This packaging configuration appears to be a unit-of-use carton. Please include a statement regarding whether or not this packaging utilizes child resistant closures.

Biovail is unclear about the intent of this request. As requested, we confirm that the carton is not child resistant, and we include a statement to that effect on the carton artwork. We also confirm, however, that the unit-dose blister *will* be child resistant. Since the request was specific to the carton, we propose to introduce language about the child-resistance of the enclosed unit dose blister cards at an appropriate time in an Annual Reportable change at or before the time of launch.

Item B.3.

Relocate the net quantity so that it does not appear in close proximity to the product strength.

Biovail agrees with the Division's request and has relocated the net quantity to a position more distant and out of register with the product strength, so as not to be mistaken for dose.

Our client Biovail Laboratories International SRL has requested that we provide this information. Should you have any questions, please do not hesitate to contact Jacqueline Little at (908) 927 – 1753.

Sincerely yours,

John F. Weet, Ph.D.
Vice President
Regulatory Affairs
Biovail Technologies Ltd.

Desk Copy: Carmen DeBellas

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908.927.1748
F 908.927.1749
jack.weet@biovail.com

2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

BIOVAIL

OVERNIGHT COURIER

April 26, 2005

Brian Harvey, MD, Acting Director
Division of Anti-inflammatory, Analgesic
And Ophthalmologic Drug Products
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA #21-693
Tramadol Hydrochloride Orally Disintegrating Tablets
Amendment: Proposed Tradename

Dear Dr. Harvey:

Reference is made to NDA #21-693 submitted to the Division on March 11, 2004 and filed on May 11, 2004, and to the Approvable Letter of January 11, 2005. The purpose of this submission is to provide a proposed tradename, as follows:

ULTRAM ® ODT (tramadol hydrochloride orally disintegrating tablets)

A letter from Ortho-McNeil Pharmaceutical, Inc. will follow this week confirming Biovail's right of reference to the Ultram tradename.

Our client Biovail Laboratories International SRL has requested that we provide this information. I trust the information provided is complete. Should you have any questions, please do not hesitate to contact Jacqueline Little at (908) 927 – 1753.

Sincerely yours,

John F. Weet, Ph.D.
Vice President
Regulatory Affairs
Biovail Technologies Ltd.

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908 927.1748
F 908 927.1749
jack.weet@biovail.com

Reedy, Kathleen R

From: Beam, Sammie
Sent: Tuesday, March 22, 2005 3:12 PM
To: Reedy, Kathleen R
Cc: Clark, Nancy
Subject: RE: NDA 21-693: (Ralivia) No-Name drug, Blister Pack

Importance: High

HI,

The following is an excerpt from the submission (March 8th from Biovail) you sent me for NDA 21-693 formerly Ralivia Flashdose with new proposed name of [redacted] ODT.
I am confused by statement #2. I am assuming the different formulation is NDA 21-692 for the extended release product. Can you clarify if the division requested two different names for the two different products? Usually in these cases the root name remains the same and the modifier changes to indicate the formulation.
Example: [redacted]
There is some concern that the sponsor may be proposing an entirely different name for the ER formulation. Can you clarify?

Thanks,
Sammie

Tradename

1. *The Division does not recommend use of the proprietary name Ralivia due to a combination of promotional inference and potential look-alike/sound-alike confusion with other products.*

2. *The Division has recommended that Biovail use two different names for the two formulations of tramadol currently under review.*

Biovail concurs, and commits to providing a different proprietary name for the other formulation under review.

March 8, 2005

Brian Harvey, MD, Acting Director
Division of Anti-inflammatory, Analgesic
And Ophthalmologic Drug Products
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-693
RALIVIA™ FLASHDOSE® (tramadol hydrochloride) Orally Disintegrating Tablets
Complete Response to FDA Approvable Letter

Dear Dr. Harvey:

Reference is made to NDA 21-693 submitted to the Division on March 11, 2004 and filed on May 11, 2004, and to the Approvable Letter of January 11, 2005. The purpose of this submission is to provide a Complete Response to all the approvability issues in the letter. This submission includes a revised label (Prescribing Information), mock-up packaging, and a proposal for a tradename that meets the requirements described in a Division letter dated January 7, 2005.

The Division's comments and concerns are paraphrased below, followed by Biovail's response.

Tradename

1. *The Division does not recommend use of the proprietary name Ralivia due to a combination of promotional inference and potential look-alike/sound-alike confusion with other products.*

2. *The Division has recommended that Biovail use two different names for the two formulations of tramadol currently under review.*

Biovail concurs, and commits to providing a different proprietary name for the other formulation under review.

Other

3. *The Division recommends that the name of our FlashDose technology not be used as a modifier, and that ODT is the acceptable modifier nomenclature in the Orange Book.*

   Biovail Response: Biovail proposes the tradename [redacted] **ODT.**

Biovail recognizes that upon agreement to a tradename, all pertinent documents, such as labeling and package labels, will be transposed to the agreed tradename, and existing documents will be considered bridged with respect to the identity of the drug product.

All other revisions requested by the Division have been incorporated into the Prescribing Information.

This electronic submission is provided on a CD that was scanned for viruses with Symantec Antivirus Corporate Edition version 3/7/2005, rev. 32 and is virus-free.

I trust the information provided is complete. Should you have any questions, please do not hesitate to contact Jacqueline Little at (908) 927 – 1753.

Sincerely yours,
On behalf of Biovail Laboratories, Inc.

Jacqueline Little
on behalf of

John R. Weet, Ph.D.
Vice President
Regulatory Affairs
Biovail Technologies Ltd.

Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908.927.1748
F 908.927.1749
jack.weet@biovail.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-693

INFORMATION REQUEST LETTER

Biovail Laboratories Incorporated/c/o Biovail Technologies Ltd.
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Weet:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ralivia Flashdose (tramadol hydrochloride) Orally Disintegrating Tablets 50 mg.

We have reviewed your trade name and have the following comments and recommendations for labeling.

We do not recommend use of the proprietary name Ralivia. The name Ralivia implies a promotional claim, that the medication will provide relief. In reviewing the proprietary name Ralivia Flashdose, concerns arose with look-alike and sound-alike confusion with Revia, Relenza, Kariva, Alinia, and Raptiva.

We do not recommend the use of a modifier. Since Ralivia ER or Ralivia Flashdose may be approved at different times, there is a potential that one drug may be on the market, while the other product is still undergoing review. If only one product with the root name Ralivia is marketed, for any timeframe, the potential for practitioners to omit the modifier increases. For example, an order could be written as, "Ralivia 50 mg qd," instead of, "Ralivia Flashdose 50 mg qd." Post-marketing error reports and independent research has indicated that the omission of modifiers continues to cause medication errors.

We do not recommend the use of a technology (flashdose) as a modifier in general, and in particular when there is a possibility that other products in the market place employ the same technology. ODT is the acceptable nomenclature in the Orange Book.

If you have any questions, call Kathleen Reedy, Regulatory Health Project Manager, at 301-827-2533.

Sincerely,

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

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

/s/

Sharon Hertz
1/7/05 11:12:28 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

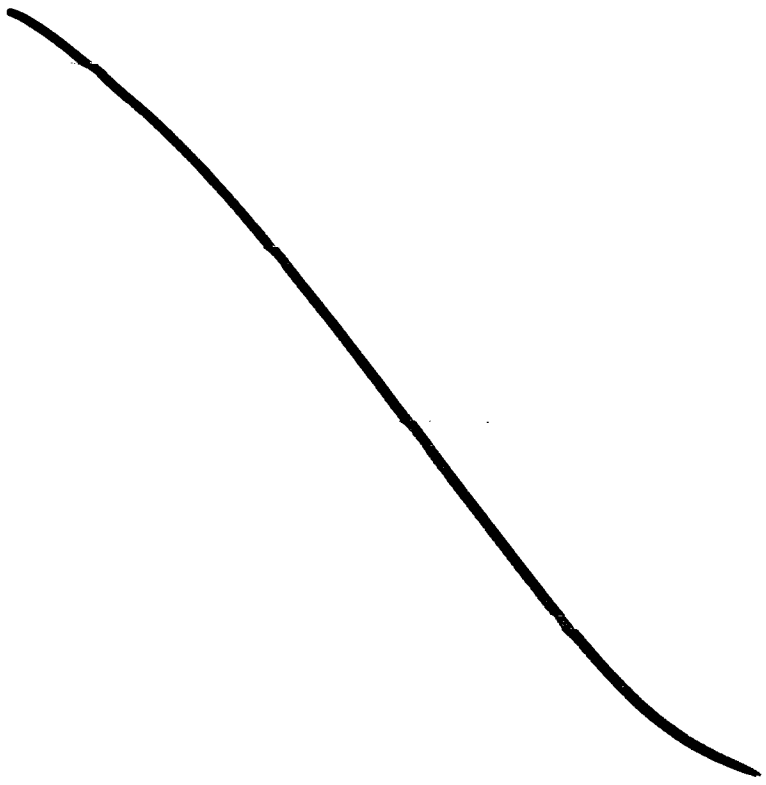
NDA 21-693
Biovail Laboratories Incorporated/c/o Biovail Technologies Ltd.
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (tramadol hydrochloride) orally disintegrating tablets, 50 mg.
We also refer to your April 14, and 20, 2005 submissions containing revised blister pack and carton labels.

We have reviewed the referenced material and have the following comments and recommendations.

A. Blister Label



If you have any questions, call Kathleen Reedy, Regulatory Health Project Manager, at 301-827-2533.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-693

Biovail Laboratories Incorporated
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride orally disintegrating tablets, 50 mg.

We have reviewed the referenced material and have the following comments and recommendations.

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 are denying your request for a waiver for pediatric studies. Pediatric studies may be deferred pending review of postmarketing safety reports following at least one year, but no more than two years, of marketing this product for adults. Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

> The minimum effective dose of tramadol hydrochloride orally disintegrating tablet, 50 mg. for the treatment of moderate to moderately severe pain in the adult population has not been adequately studied to allow extrapolation into the pediatric population without robust efficacy studies in children.

If you have any questions, call Kathleen Reedy, Regulatory Health Project Manager, at 301-827-2533.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
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

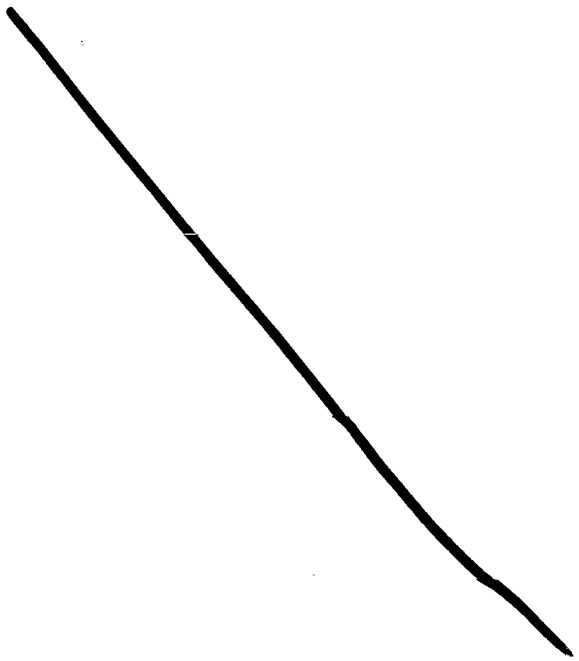
NDA 21-693
Biovail Laboratories Incorporated/c/o Biovail Technologies Ltd.
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Weet:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ralivia (tramadol HCl) orally disintegrating tablets.

We have reviewed the referenced material and have the following comments and recommendations for labeling.

General



1 Page(s) Withheld

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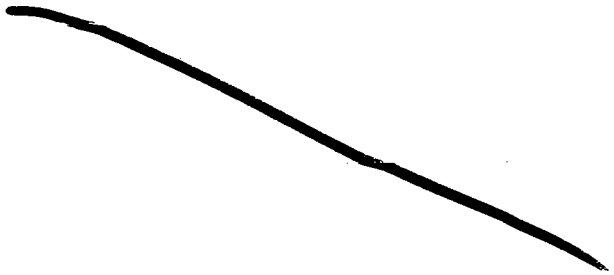
✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3



If you have any questions, call Kathleen Reedy, Regulatory Health Project Manager, at 301-827-2533.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
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

FILING COMMUNICATION

NDA 21-693

Biovail Laboratories, Inc.
Attention: John B. Dubeck, U. S. Agent
Vice President, Regulatory Affairs
1001 G Street, N.W., Suite 500-W
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your March 10, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ralivia – Flashdose, (tramadol hydrochloride) Orally Disintegrating Tablets, 50 mg.

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 May 10, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call Kathleen Reedy, Regulatory Project Manager, at (301) 827 2533.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management
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 21-693

Biovail Laboratories, Inc.
Attention: John F. Weet, Ph.D.,
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, New Jersey 08807

Dear Dr. Weet:

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 FlashDose (tramadol hydrochloride) orally disintegrating tablets, 50 mg.

Review Priority Classification: Standard (S)

Date of Application: March 10, 2004

Date of Receipt: March 11, 2004

Our Reference Number: NDA 21-693

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 May 11, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 11, 2005.

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.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Fax

DATE: 12/15/04

TO: Jacqueline Little, Director Regulatory Liaison, Biovail Laboratories, Inc.
Fax: 908-927-1553 **Phone:** 908-927-1753

FROM: Kathleen Reedy, RDH, MS, Regulatory Health Project Manager
Fax: 301-827-2531 **Phone:** 301-827-2533

RE: New Comments to NDA 21-693 from Chemistry

TOTAL PAGES: 2 ☑ **URGENT** ☐ **PLEASE REPLY** ☐ **FOR REVIEW ONLY**

Jacqueline, please provide us with a response. Thanks! You can fax it and then submit it to the NDA.

Kathleen

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Fax

DATE: 12/14/04

TO: Jacqueline Little, Director Regulatory Liaison, Biovail Laboratories, Inc.
Fax: 908-927-1553 **Phone:** 908-927-1753

FROM: Kathleen Reedy, RDH, MS, Regulatory Health Project Manager
Fax: 301-827-2531 **Phone:** 301-827-2533

RE: Comments to NDA 21-693 from Chemistry

TOTAL PAGES: 2 ☑ **URGENT** ☐ **PLEASE REPLY** ☐ **FOR REVIEW ONLY**

Jacqueline, please provide us with a response. Thanks! You can fax it and then submit it to the NDA.

Kathleen

1. **Please provide the rationale for setting tablet disintegration time at [redacted] Since stability data indicated all were disintegrated within [redacted] we recommend setting the limit at 30 seconds.**

2. **Assay limits of [redacted] seem broad. We recommend that the limit be tightened.**

<<NDA 21-693-FDA fax 14Dec04.pdf>>
Response to faxed 2 Chemistry questions

Dear Kathleen,

As a follow-up to your fax sent yesterday (above), our CMC team has proposed the following response:

1. We concur that a specification of 30 seconds for disintegration performed [redacted] is acceptable.

2. We agree that the in-process specification can be tightened based on available data. Biovail proposes the following specification: [redacted]

If Biovail's response is acceptable to the Division CMC reviewers, please let us know and we will begin change control procedures. In view of the time remaining until the PDUFA date (January 11), is this commitment sufficient?

Thank you.

> Best regards,
> Jacqueline Little, M.Sc.
> Director, Regulatory Liaison
> CNS & Pain
> Biovail Technologies, Ltd.
> 700 Routes 202/206 North
> Bridgewater, NJ 08807
> Tel 908-927-1753
> Mobile 908-216-1190
> Fax 908-927-1553
> e-mail: Jacqueline.Little@biovail.com
>

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

/s/

Kathleen Reedy
12/15/04 11:59:52 AM
CSO

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Fax

DATE: 11/23/04

TO: Jacqueline Little, Director Regulatory Liaison, Biovail Laboratories, Inc.
Fax: 908-927-1553 **Phone:** 908-927-1753

FROM: Jane Dean, RN, MSN, Regulatory Health Project Manager
Fax: 301-827-2531 **Phone:** 301-827-2536

RE: Request for Information for NDA 21-693 from Chemistry

TOTAL PAGES: 2 ☑ **URGENT** ☐ **PLEASE REPLY** ☐ **FOR REVIEW ONLY**

Jacqueline, can you please provide us with a response asap? Thanks! You can fax it to us and then send it out as a formal submission to the NDA.

Sincerely,

Jane Dean

1. Please provide the rationale for setting tablet hardness [redacted]. Is there any relationship between tablet hardness and rate of tablet disintegration? Please explain.

2. Acceptance criteria for tablet friability were not established. Please explain.

3. Identification by HPLC only is considered insufficient (see the recommendations in ICH guidance Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances). Please provide at least one additional ID test to assure the identification of the drug substance.

4. The following comments pertain to the twelve months of stability data submitted on November 9, 2004:

a. The stability data submitted for lots manufactured and packaged at [redacted] failed to provide tests result for tablet disintegration at each test station. Since the disintegration behavior of these tablets is a critical performance characteristic, the absence of these results diminishes the value of the study results.

b. For lots packaged at [redacted] test results for tablet disintegration were merely stated as "Complies." Please provide actual test results (i.e., numerical data).

5. Assuming that the missing data from stability data for the lots packaged in [redacted] can be provided and is acceptable, we propose that you use an [redacted] month expiration dating period.

IND 66,859 **Meeting Request Submission Date:** July 07, 2003,
Briefing Document Submission Date: September 11, 2003 SN 002

DRUG: Tramadol HCl Immediate Release Orally Disintegrating Tablets (ODT), 50 mg

APPLICANT: Biovail Technologies, Ltd.

QUESTIONS with FDA RESPONSE:

Clinical Pharmacology:

One pilot pharmacokinetic study has been conducted during the development cycle. In addition, a pivotal fasting study and a pivotal food-effect study are being conducted to support the NDA filing.

Question 1- Does the agency agree that the proposed fasting and food-effect studies will be sufficient to support the Tramadol HCl ODT Tablets new drug application?

FDA Response:

Provided that the pilot study (e.g., BA and with and without water) was done and pivotal studies will be done with the to be marketed study material then these studies would be supportive of an NDA application. Whether or not they would be "sufficient to support registration and labeling" is ultimately a review issue that and cannot be addressed at this time. Please note the following comments:

Food Effect Study: As the intent of the dosage form (ODT) is to take without water or any other liquid, the sponsor is encouraged to administer the dosage form in the food effect study without water. Also, the sponsor is encouraged to recruit fairly equal number of male and female subjects in the study.

***In vivo/In vitro* Disintegration Time: The sponsor is encouraged to submit both *in vitro* and *in vivo* disintegration time data in the NDA submission. For *in vitro* study, simulated saliva medium will be preferred.**

***In vitro* Dissolution Time: For *in vitro* study, simulated saliva medium will be preferred.**

Pre-clinical Toxicology:

Biovail has conducted pre-clinical toxicology studies, using the active pharmaceutical ingredient,

Question 2- Does the Agency agree

[redacted]

CMC information:

A minimum of six months accelerated (40°C/75%RH) and 6 months room temperature (25°C/60%RH) stability data for 4 lots of Tramadol HCl ODT Tablets in blisters, as well as a minimum of 2 months stability data for lots manufactured at the commercial facility will be available at the time of NDA submission.

Question 3- Does the Agency concur that the stability data submitted are sufficient for the Agency to grant an expiry date of [redacted] months at the time of approval?

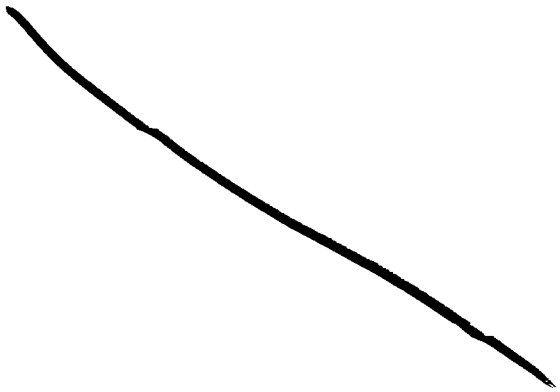
FDA Response:

Please provide comparative dissolution profiles and accelerated stability data for batches manufactured at the two locations. Each dissolution profile should contain at least three time points (four time points are preferred), not more than one of which should be along the asymptote.

According to ICH Guidance Q1C, a reduced stability database at the time of submission (e.g., 6 months of data under accelerated and long term conditions) may be acceptable in certain cases if justified. Please provide a justification for submitting such a reduced stability database for this product. Regardless of how much stability data will be submitted in your application, we cannot comment on the acceptability of a [redacted] month expiration period at this time. The establishment of an expiration period for a drug product is a review issue that depends on a number of factors, including the number of lots of drug product on stability, the duration of the studies, and the quality of the stability data.

ADDITIONAL CMC COMMENTS:

[redacted]



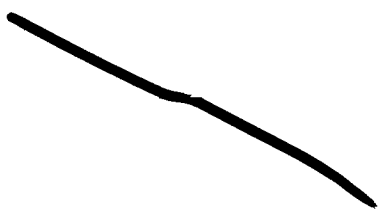
Question 4- Will an API impurity profile consistent with that of the primary supplier, and acceptable impurity, dissolution and stability testing from one lot of finished product manufactured using API from the alternate supplier be sufficient to support the approval of the alternate supplier?

FDA Response:

The information submitted to support an alternative drug substance supplier should include:

- **comparative dissolution profiles (one lot of drug product manufactured with drug substance from the alternative supplier compared to drug product manufactured with drug substance from the primary supplier),**
- **at least 3 months of stability data on 3 lots of drug substance from the alternative drug substance supplier,**
- **comparative data on impurities in drug substance manufactured by the two suppliers, and**
- **a reference to the alternative supplier's DMF.**

Proposed Labeling (PI):



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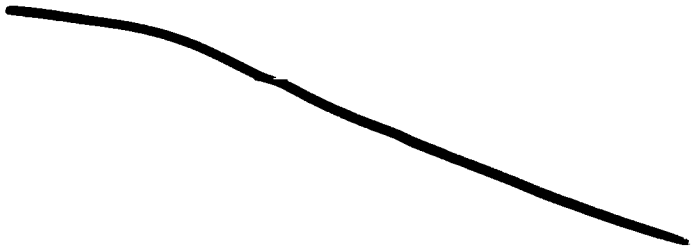
✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4



Administrative 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 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".

Barbara Gould 03 Nov. 2003
Barbara Gould Date
Project Manager

Concurrence Chair: *Lee S. Simon, M.D.03 Nov. 2003*
Lee S. Simon, M.D. Date
Director

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

/s/

Lee Simon
11/5/03 01:32:17 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: December 31, 2006.

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

Ralivia™ FlashDose®(tramadol hydrochloride orally disintegrating tablets)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021693

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® (tramadol hydrochloride) NDA 20-281
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

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 FOR THIS 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
[signature]	Vice President, Regulatory Affairs	03/10/2004

FORM FDA 3397 (12/03)

PSC Media Arts (301) 443-1090 EF

NDA REGULATORY FILING REVIEW

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

NDA #: _____

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): 20-281, Ultram

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☒

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☒

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change in strength, 50 mg, and absorptive action, ODT.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☒ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☒ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☒ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES ☒ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A ☐ YES ☒ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A ☐ YES ☐ NO ☒

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☒ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☒

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# [redacted] _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☒ NO ☐

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-693** Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Ralivia -Flashdose**
Generic Name: **tramadol hydrochloride orally disintegrating tablets**
Strengths: **50 mg.**

Applicant: **Biovail Laboratories, Inc.**

Date of Application: **10 March 2004**
Date of Receipt: **11 March 2004**
Date clock started after UN: **11 March 2004**
Date of Filing Meeting: **3 May 2004**
Filing Date: **10 May 2004**
Action Goal Date (optional): **11 November 2004** User Fee Goal Date: **11 January 2004**

Indication(s) requested: **treatment of moderate to moderately severe pain**

Type of Original NDA: (b)(1) _____ (b)(2) **XX**
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: 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). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S **XX** P _____
Resubmission after withdrawal? NA Resubmission after refuse to file? NA
Chemical Classification: (1,2,3 etc.) **3**
Other (orphan, OTC, etc.) NA

User Fee Status: Paid _____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) XX 505 (b)(2)

Form 3397 (User Fee Cover Sheet) submitted: **YES** NO
User Fee ID # **N021693**
Clinical data? YES _____ NO, **Referenced to NDA # 20-281 Ultram**

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES **NO**

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NA YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? **NA** YES NO

- Does the submission contain an accurate comprehensive index? **YES** NO
- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES** NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A **YES** NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? submissions only

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO
- Is it an electronic CTD? **N/A** YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? **YES** NO
- Exclusivity requested? YES, _____years **NO**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] 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."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? **YES** NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **IND 66,859**

- End-of-Phase 2 Meeting(s)? Date(s) _____
- If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? **Date(s) 10 Oct 2003**
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **YES** NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application: **NA**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **NA**
  YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES** NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? **YES** NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES **NO**

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: **Ultram, 20-281**
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application is for a new dosage form, an orally disintegrating tablet that may be taken with or without water.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES **NO**

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES **NO**

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES **NO**

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.
  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.
  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.
  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  X 21 CFR 314.50(i)(1)(ii): No relevant patents.
  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.
  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES **NO**

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A **YES** NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES **NO**

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # **66,859** NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 3, 2004

BACKGROUND:
Biovail Laboratories, Inc. has submitted an NDA for Ralivia FlashDose (tramadol hydrochloride) an Orally Disintegrating Tablet, 50 mg., that may be taken with or without water. This is a new dosage form of the referenced drug Ultram, NDA 20-281.

ATTENDEES: Harvey, Brian; Schiffenbauer, Joel; Smith, John L; Bashaw, Edward D; Witter, James P; DeBellas, Carmen; Bull, Jonca; Rumble, Terri F; Thomas, Ho, Bartholome C; Mukherjee, Asoke; Kim, Yongman; Dean, Jane; Ghosh, Tapash

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Joel Schiffenbauer
Secondary Medical:	Tatiana Oussova
Statistical:	Yongman Kim
Pharmacology:	Asoke Mukherjee
Statistical Pharmacology:	
Chemistry:	Bart Ho
Environmental Assessment (if needed):	
Clinical Pharmacology:	Tapash Ghosh
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Kathleen Reedy
Other Consults:	

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL FILE __X____ REFUSE TO FILE _____

- Clinical site inspection needed: YES **NO**
- Advisory Committee Meeting needed? YES, date if known _____ **NO**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY **NA** __X____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE __X____ REFUSE TO FILE

CLINICAL PHARMACOLOGY FILE __X____ REFUSE TO FILE

- Biopharm. inspection needed: YES **NO**

PHARMACOLOGY NA _____ FILE __X____ REFUSE TO FILE

- GLP inspection needed: YES **NO**

CHEMISTRY FILE __X____ REFUSE TO FILE

- Establishment(s) ready for inspection? YES **NO**
- Microbiology YES **NO**

ELECTRONIC SUBMISSION: **YES**
Any comments: NO

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

__X____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. **Document filing issues/no filing issues conveyed to applicant by Day 74. Yes**

__Kathleen R. Reedy, RDH, MS_____
Regulatory Project Manager, HFD-550

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

/s/

Kathleen Reedy
6/9/04 04:56:12 PM
CSO

Kathleen Reedy
6/9/04 04:57:22 PM
CSO

NDA ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-693	Efficacy Supplement Type SE- NA	Supplement Number N/A	
Drug: Ralivia FlashDose		Applicant: Biovail Laboratories	
RPM: Kathleen Reedy		HFD-550	Phone # (301) 827-2533

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 (tramadol hydrochloride)

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3 S
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Dates	January 11, 2005 (AE) May 8, 2005 (AP)
❖ 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	NA
• User Fee	( ) Paid UF ID number _____
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) _____
• User Fee exception	( ) Orphan designation (X) 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)	NA
• OC clearance for approval	NA
❖ 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) (X) Verified Paragraph IV 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).	**NA**
• [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).*	(X) Yes ( ) No ( ) Yes ( ) No

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (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.*	( ) Yes ( ) No
(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).*	( ) Yes **(X)** No
(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.*	( ) Yes **(X)** 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.)	See Summary
• 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 #_____ **(X)** No

❖ ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Filing Meeting: 5/3/04 Filing Review: 5/10/04 Appendix B: 5/4/05
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE: 1/11/05
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) 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)	December 20, 2004
• Most recent applicant-proposed labeling	January 10, 2005
• Original applicant-proposed labeling	3/10/04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: 7/12/04 DDMAC: 11/16/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	None submitted
• Applicant proposed	1/12/05; 4/14/05; 4/20/05, 5/3/05
• Reviews	DDMAC: 2/2/05 DMETS: 4/11/05, 5/4/05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	3/24/04; 5/10/04; 11/23/04; 12/14/04; 12/15/04; 12/20/04; 1/7/05; 1/11/05; 1/14/05; 4/27/05, 4/28/05
❖ Memoranda and Telecons	5/10/04; 5//18/04; 11/8/04; 1/11/05; 1/12/05/ 3/4/05; 4/5/05, 4/28/05, 5/3/05
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	October 14, 2003 (cancelled)
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader, 1/4/05 Deputy Division Director, 1/11/05, 5/4/05
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	12/21/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	12/21//04 Clinical Review, Pg 4
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	3/10/04 waiver,
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	NA, no new clinical trials
❖ Biopharmaceutical review(s) *(indicate date for each review)*	12/12/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	10/1/04
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	12/23/04, 3/18/05
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: 12/21/04 **(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)*	December 13, 2004
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

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).