

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-693

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 18, 2005

TO: Kathleen Reedy, program manager

FROM: Bart Ho

SUBJECT: **Carton Labeling**
NDA 21-693, None (Tramadol HCL) ODT

We examined the carton label and found it is acceptable.

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

/s/

Bartholomew Ho
3/18/05 03:56:52 PM
CHEMIST

John Smith
3/18/05 04:04:26 PM
CHEMIST

NDA 21-693

**Tramadol HCl Orally Disintegrating Tablets, 50 mg
Biovail Laboratories, Inc.**

Bart Ho

Review Chemist

**Division of Anti-Inflammatory, Analgesic, and Ophthalmic
Drugs, HFD-550**

Executive Summary Section

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Chemistry Review Data Sheet

1. NDA 21-693
2. REVIEW #: 1
3. REVIEW DATE: 12/7/04
4. REVIEWER: Bart Ho
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	3-11-04
Amendment 1	11-9-04
Amendment 2	12-13-04
Amendment 3	12-14-04
Amendment 4	12-16-04
Amendment 5	12-20-04

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories, Inc.
Chelston Park, Building 1, Ground Floor,
Address: Collymore Rock, St. Michael, Barbados, West
Indies
Representative: John Dubeck, Agent
Telephone: 202-434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: FlashDose/Ralivia

b) Non-Proprietary Name (USAN):

Tramadol HCl

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c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
505(b)(2)

10. PHARMACOL. CATEGORY:

Management of moderate to moderately severe pain in adults

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY:

Tramadol HCl, 50 mg

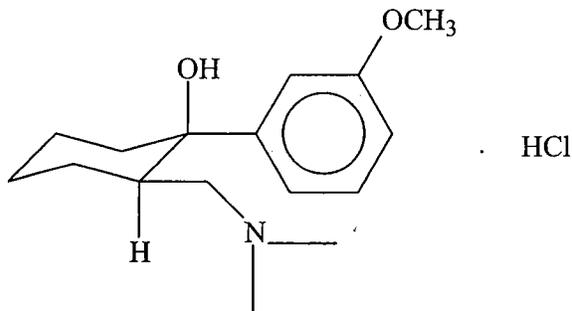
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:



(±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol HCl
Molecular Formula: C₁₆H₂₅NO₂·HCl



Executive Summary Section

Molecular Weight: 299.84

17. RELATED/SUPPORTING DOCUMENTS: N/A

A. DMFs: See table below

DMF	Type	Holder	Item Referenced	Code	Status	Date Review Completed	Comments
	II			1	Adequate	12/17/04	None
	II			3	Adequate	5/14/01	None
	III			3	Adequate	9/15/00	None
	IV			3	Adequate	8/16/04	None
	IV			7	Adequate	11/19/04	See page 15

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

B. Other Documents:

18. STATUS: None

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharm	N/A		
EES	Acceptable		
Pharm/Tox	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion		
Microbiology	N/A		



The Chemistry Review for NDA 21-693

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the chemistry point of view, NDA 21-693 may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

a. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Substances

Tramadol HCl:

Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7. [REDACTED]

[REDACTED] The desired drug substance, tramadol HCl, are a pair of enantiomers of (\pm) cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The chemical structure is shown below. [REDACTED]

[REDACTED] Tramadol HCl drug substance will be supplied by two manufacturers, [REDACTED] Manufacture and control of the drug substance were referenced, respectively, to the drug master files [REDACTED] and [REDACTED]

DMF [REDACTED]

The date of the last review was 9/5/2001. The conclusion of the review was "adequate". This reviewer reviewed the most recent amendment dated 6/4/2003. The conclusion of the review was adequate. See DMF review for details.

DMF [REDACTED] : Adequate (reviewed on May 14, 2001).

Chemistry Review Data Sheet

2) Drug Product

RALIVIA FLASHDOSE, which is applicant's proposed name for the drug product, is supplied as orally disintegrating tablets containing 50 mg of tramadol hydrochloride for oral administration. The tablets are white in color and contain the inactive ingredients aspartame, copovidone, crospovidone, ethylcellulose, magnesium stearate, mannitol, mint flavor, and silicon dioxide.



RALIVIA® FLASHDOSE® (tramadol hydrochloride orally disintegrating tablets) - 50 mg (white, tablet) debossed with "B" on one side and "50" on the other side.

Tramadol Hydrochloride Orally Disintegrating Tablets, 50 mg will be marketed in blister packaging of 6. foil/foil blisters of 10x10.

There are basically no differences in the formulations of the batches on stability, on clinical trial and batches proposed for marketing. The drug product was fully disintegrated in vitro within 30 seconds.

b. Description of How the Drug Product is Intended to be Used

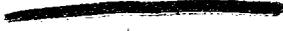
RALIVIA FLASHDOSE is indicated for the management of moderate to moderately severe pain in adults.

For adult patients (17 years of age and over) with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, RALIVIA FLASHDOSE may be started at a dose of 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, RALIVIA FLASHDOSE 50 mg to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg per day**.

c. Basis for Approvability or Not-Approval Recommendation

Based on the chemistry point of view, NDA 21-693 may be approved.

Stability data indicated that the drug product was stable for the period studied (12 months at 25°C/60%RH). Little or no degradation was found. The drug product was well disintegrated within 30 seconds. The proposed dissolution criterion specified at  in 30 minutes was deemed adequate, based on the dissolution data provided. The drug product was more than  dissolved at 30 minute.

The primary drug substance tramadol HCl supplier is  Tramadol HCl will alternatively be supplied by  All the facilities specified in the application have been found acceptable by compliance.

33 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

Bartholomew Ho
12/23/04 12:03:00 PM
CHEMIST

John Smith
12/23/04 12:09:29 PM
CHEMIST