CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

CHEMISTRY REVIEW(S)

NDA 21-692

Tramadol HCl ER Tablet, 100, 200, and 300 mg
Biovail Laboratories, Inc.

Bart Ho

Review Chemist

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-692

2. REVIEW #2:

3. REVIEW DATE: 8/22/05

4. REVIEWER: Bart Ho

5. PREVIOUS DOCUMENTS: N/A

Original	12-31-03
Amendment 1	8-30-04 (stability data update)
Amendment 2	9-8-04 (response to FDA)
Amendment 3	10-13-04 (facility withdrawn)
Amendment 4	10-28-04 (response to FDA)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 5	3-7-05
Amendment 6	8-16-05
Amendment 7	8-17-05
Amendment 8	8-23-05

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a)Proprietary Name: None submitted at the time of review.

b)Non-Proprietary Name (USAN): Tramadol HCl ER

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

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

- Chem. Type: 5
- 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: Tablet, Extended Release

12. STRENGTH/POTENCY: Tramadol HCl, 100 mg, 200 mg, and 300 mg

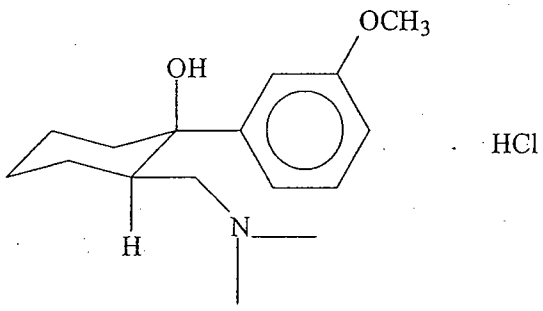
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

_____SPOTS product – Form Completed
___x___Not a SPOTS product

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



Molecular Formula: $C_{16}H_{25}NO_2 \cdot HCl$
Molecular Weight: 299.84

17. RELATED/SUPPORTING DOCUMENTS: N/A

Executive Summary Section

A. DMFs: See table below

DMF	Type	Holder	Item Referenced	Code	Status	Date Review Completed	Comments
	II		Tramadol HCl DS	3	Adequate	3/25/04	None
	II		Tramadol HCl DS	1	Adequate	10/12/04	None
	II		Tramadol HCl DS	7	Adequate	6/14/04	Withdrawn
	III			3	Adequate	9/15/00	None
	III			3	Adequate	9/27/00	None
	III			3	Adequate	5/27/03	None
	III			3	Adequate	4/3/01	None
	III			3	Adequate	5/5/01	None
	III			3	Adequate	10/20/03	None
	III			3	Adequate	1/4/00	None
	III			3	Adequate	1/7/04	None
	III			3	Adequate	11/18/02	None
	III			3	Adequate	8/16/04	None

[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	To be inspected		
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 21-692

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval based on the chemistry point of view.

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

N/A

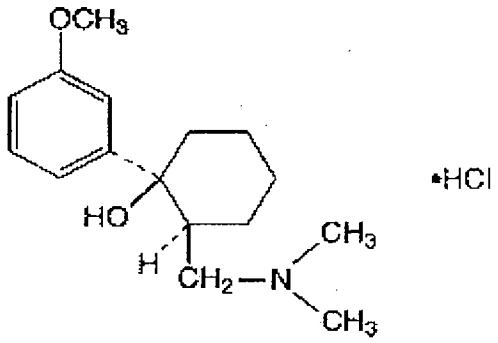
II. Summary of Chemistry Assessments

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

1) Drug Substances

Tramadol HCl:

Tramadol HCl contains two asymmetric centers, therefore, has four stereoisomers. The desired drug substance, tramadol HCl, are a pair of enantiomers of (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The chemical structure is shown below. The other two stereoisomers are (±) trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. They are impurities if present. The tramadol HCl can also be described as (±)-(RR, SS)-2-[(Dimethylamino) methyl]-1-(3 methoxyphenyl)-cyclohexanol Hydrochloride.



Tramadol HCl drug substance initially was going to be supplied by [redacted] manufacturers namely, [redacted]. Manufacture and control of the drug substance were referenced, respectively, to drug master files [redacted]. Biovail withdrew [redacted] as API supplier on 10-13-04.

Review of DMF:

DMF —— Adequate

The most recent review of this DMF was review #4 dated 3/25/04 for ANDA 76-914. Conclusion of the review was "Adequate". No amendment was submitted after this review.

DMF —— Adequate

The DMF has been reviewed and was found inadequate initially. The Drug Substance supplier responded to the DMF deficiencies. The amendment to the DMF was reviewed and found adequate.

DMF —— : Adequate

The most recent review of the DMF was review #2 dated 9/26/01. The DMF was found adequate. The DMF was amended on 12/26/02. The amendment was reviewed by this reviewer and was found adequate.

Note: Biovail withdrew —— as API supplier on 10-13-04.

2) Drug Product

Tramadol Hydrochloride Extended-Release Tablets, 100 mg, 200 mg and 300 mg are diffusion controlled tablets consisting of a tablet core surrounded by a semi-permeable coating. This coating forms a membrane that is responsible for controlling the release of tramadol hydrochloride in vivo. Tramadol hydrochloride Extended-Release Tablets, 100 mg, are white to off-white round tablets imprinted with "B" on one side and "100" on the other side in black ink. Tramadol Hydrochloride Extended-Release Tablets, 200 mg, are white to off-white round tablets imprinted with "B" on one side and "200" on the other side in black ink. Tramadol Hydrochloride Extended-Release Tablets, 300 mg, are white to off-white round tablets imprinted with "B" on one side and "300" on the other side in black ink.

Tramadol Hydrochloride Extended-Release Tablets, 100 mg, 200 mg and 300 mg will be marketed in the packaging formats in bottles of 4's and 500's in white opaque round —— bottles, 30's and 90's in white opaque square —— bottles and foil/foil blisters of 10x10.

There are basically no differences in the formulations of the three strengths proposed for marketing and the formulation on clinical trial. Due to rapid dissolution of the drug product, the particle size of the tramadol HCl drug substance is not considered an important attribute.

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

For adult patients (18 years of age and over) with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect. Tramadol HCl ER tablets should be administered for pain relief at a dose not to exceed — mg/day.

In patients over 75 years of age, daily doses in excess of 300 mg are not recommended.

The safety and efficacy of Tramadol HCl ER tablets in patients under 18 years of age have not been established. The use of Tramadol HCl ER tablets in the pediatric population is not recommended.

c. Basis for Approvability or Not-Approval Recommendation

Recommend approval for NDA 21-692 based on the chemistry point of view.

Stability data indicated that the drug product was stable for the period studied. Little or no degradation was found for up to the 36 month storage period. Potencies varied; however, there was no evidence of a trend in decreasing in potency for the period studied. With the submission of up to 36 months satisfactory room temperature (25°C/60% RH) stability data on pivotal stability batches, firm's request for 24 months expiration date for drug products stored at room temperature (25°C/60% RH) in the proposed container/closure systems is acceptable.

The proposed dissolution criterion specified at 2, 4, 8, and 16 hours are deemed adequate based on the dissolution data provided. The dissolution rate at the end of 16 hours was not less than — Acceptability of the dissolution ranges at 2, 4, 8 and 16 hours will be reviewed by the Biopharm reviewer.

Concern was raised whether the release of drug from these tramadol HCl ER tablets might be accelerated — if they were taken with alcohol. Firm conducted dissolution testing on 100 mg, 200 mg, and 300 mg products with test media containing a mixture of — . The methodology and the parameters used for the study remained the same. FDA concluded, after reviewing the data that this product did not show significant dose — in the in vitro dissolution testing with — in the medium.

III. Administrative

a. Reviewer's Signature

b. Endorsement Block

c. CC Block

31 Page(s) Withheld

9 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-_____

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
8/29/2005 05:28:13 PM
CHEMIST

John Smith
8/30/2005 08:58:24 AM
CHEMIST

NDA 21-692

Ralivia ER(Tramadol HCl) Tablet, 100/200/300 mg
Biovail Laboratories, Inc.

Bart Ho

Review Chemist

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-692

2. REVIEW #: 1

3. REVIEW DATE: 10/18/04

4. REVIEWER: Bart Ho

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12-31-03
Amendment 1	8-30-04 (stability data update)
Amendment 2	9-8-04 (response to FDA)
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Representative:	John Dubeck, Agent
Telephone:	202-434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

a)Proprietary Name: Ralivia ER

b)Non-Proprietary Name (USAN):

Tramadol HCl ER

Executive Summary Section

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

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

- Chem. Type: 4
- 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: Tablet, Extended Release

12. STRENGTH/POTENCY: Tramadol HCl, 100 mg, 200 mg, and 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

_____SPOTS product – Form Completed
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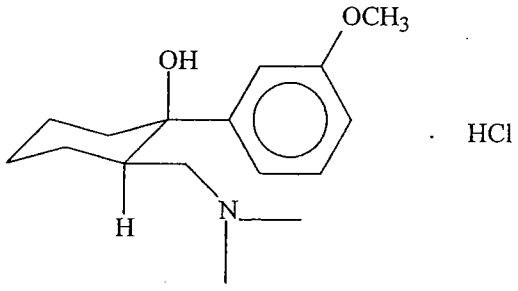

Molecular Formula: $C_{16}H_{25}NO_2 \cdot HCl$
Molecular Weight: 299.84

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	III			3	Adequate	9/27/00	None
	III			3	Adequate	5/27/03	None
	III			3	Adequate	4/3/01	None
	III			3	Adequate	5/5/01	None
	III			3	Adequate	10/20/03	None
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B. Other Documents:

18. STATUS: None

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

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-692

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the chemistry point of view, NDA 21-692 is approvable. The sponsor should provide a satisfactory response to the deficiency forwarded to the sponsor.

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

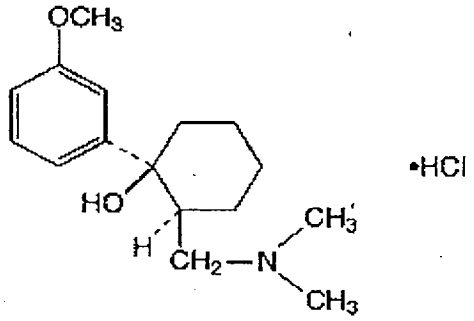
II. Summary of Chemistry Assessments

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

1) Drug Substances

Tramadol HCl:

Tramadol HCl contains two asymmetric centers, therefore, has four stereoisomers. The desired drug substance, tramadol HCl, are a pair of enantiomers of (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The chemical structure is shown below. The other two stereoisomers are (±) trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. They are impurities if present. The tramadol HCl can also be described as (±)-(RR, SS)-2-[(Dimethylamino) methyl]-1-(3 methoxyphenyl)-cyclohexanol Hydrochloride.



Tramadol HCl drug substance initially was going to be supplied by [redacted] manufacturers [redacted] Manufacture and control of the drug substance were referenced, respectively, to drug master files [redacted]. Biovail withdrew [redacted] as API supplier on 10-13-04.

Chemistry Review Data Sheet

Review of DMF:

DMF — Adequate

The most recent review of this DMF was review #4 dated 3/25/04 for ANDA 76-914. Conclusion of the review was "Adequate". No amendment was submitted after this review.

DMF — **Inadequate**

The DMF has been reviewed and was found inadequate. A deficient letter has been forwarded to the sponsor for response.

Biovail response:

The Drug Substance supplier, — has informed Biovail that they submitted a written response to the DMF deficiencies in July, 2004.

Evaluation:

The amendment to the DMF has been reviewed and was found adequate.

DMF — : Adequate

The most recent review of the DMF was review #2 dated 9/26/01. The DMF was found adequate. The DMF was amended on 12/26/02. The amendment was reviewed by this reviewer and was found adequate.

Note: Biovail withdrew — as API supplier on 10-13-04.

2) Drug Product

Tramadol Hydrochloride Extended-Release Tablets, 100 mg, 200 mg and 300 mg are diffusion controlled tablets consisting of a tablet core surrounded by a semi-permeable coating. This coating forms a membrane that is responsible for controlling the release of tramadol hydrochloride in vivo. Tramadol hydrochloride Extended-Release Tablets, 100 mg, are white to off-white round tablets imprinted with "B" on one side and "100" on the other side in black ink. Tramadol Hydrochloride Extended-Release Tablets, 200 mg, are white to off-white round tablets imprinted with "B" on one side and "200" on the other side in black ink. Tramadol Hydrochloride Extended-Release Tablets, 300 mg, are white to off-white round tablets imprinted with "B" on one side and "300" on the other side in black ink.

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There are basically no differences in the formulations of the three strengths proposed for marketing and the formulation on clinical trial. Due to rapid dissolution of the drug product, the particle size of the tramadol HCl drug substance is not considered an important attribute.

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

For adult patients (18 years of age and over) with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, Ralivia ER should be administered for pain relief at a dose not to exceed [redacted] /day.

In patients over 75 years of age, daily doses in excess of 300 mg are not recommended.

The safety and efficacy of Ralivia ER in patients under 18 years of age have not been established. The use of Ralivia ER in the pediatric population is not recommended.

c. Basis for Approvability or Not-Approval Recommendation

Based on the chemistry point of view, NDA 21-692 is approvable.

Stability data indicated that the drug product was stable for the period studied. Little or no degradation was found for up to the 36 month storage period. Potencies varied; however, there was no evidence of a trend in decreasing in potency for the period studied. The proposed dissolution criterion specified at 2, 4, 8, and 16 hours are deemed adequate based on the dissolution data provided. The dissolution rate at the end of 16 hours was not less than [redacted]. Acceptability of the dissolution ranges at 2, 4, 8 and 16 hours will be reviewed by the Biopharm reviewer.

The primary drug substance, tramadol HCl supplier is [redacted] Tramadol HCl drug substance [redacted]. All the facilities specified in the application have been scheduled to be inspected. The [redacted] API suppliers were qualified by the submission of satisfactory comparative dissolution profiles for drug products manufactured by using tramadol HCl purchased from the [redacted] APIs. However, [redacted] was withdrawn from the application on 10-13-04.

With the submission of up to 36 months satisfactory room temperature (25°C/60% RH) stability data on pivotal stability batches, firm's request for 24 months expiration date for drug products stored at room temperature (25°C/60% RH) in the proposed container/closure systems is acceptable.

III. Administrative

a. Reviewer's Signature N/A

b. Endorsement Block N/A

c. CC Block N/A

26 Page(s) Withheld

26 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-_____

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
10/18/04 01:39:22 PM
CHEMIST

John Smith
10/18/04 01:54:34 PM
CHEMIST