

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-763

CHEMISTRY REVIEW(S)



NDA 21-763

**TradeName™ (Citalopram Hydrobromide)
Orally Disintegrating Tablets**

Biovail Technologies, Ltd.

Lyudmila N. Soldatova, Ph.D.

***DIVISION OF NEUROPHARMACOLOGICAL DRUG
PRODUCTS***

Review of Chemistry, Manufacturing, and Controls



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I. DRUG SUBSTANCE	N/A
1. Description & Characterization	N/A
a. Description	N/A
b. Characterization / Proof Of Structure	N/A
2. Manufacturer	N/A
3. Synthesis / Method Of Manufacture	N/A
a. Starting Materials - Specs & Tests.....	N/A
b. Solvents, Reagents, etc	N/A



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c. Flow Chart.....	N/A
d. Detailed Description.....	N/A
4. Process Controls.....	N/A
a. Reaction Completion / Other In-Process Tests.....	N/A
b. Intermediate Specs & Tests.....	N/A
5. Reference Standard	N/A
a. Preparation	N/A
b. Specifications.....	N/A
6. Regulatory Specifications / Analytical Methods	N/A
a. Drug Substance Specifications & Tests	N/A
b. Purity Profile.....	N/A
c. Microbiology.....	N/A
7. Container/Closure System For Drug Substance Storage.....	N/A
8. Drug Substance Stability.....	N/A
II. DRUG PRODUCT
1. Components/Composition	N/A
2. Specifications & Methods For Drug Product Ingredients	N/A
a. Active Ingredient(s).....	N/A
b. Inactive Ingredients	N/A
3. Manufacturer	N/A
4. Methods Of Manufacturing And Packaging	N/A
a. Production Operations.....	N/A
b. In-Process Controls & Tests.....	N/A
c. Reprocessing Operations	N/A
5. Regulatory Specifications And Methods For Drug Product.....	N/A
a. Sampling Procedures	N/A
b. Regulatory Specifications And Methods	N/A
6. Container/Closure System.....	N/A
7. Microbiology.....	N/A
8. Drug Product Stability	N/A
III. INVESTIGATIONAL FORMULATIONS	N/A



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- IV. ENVIRONMENTAL ASSESSMENT.....N/A
- V. METHODS VALIDATION.....N/A
- VI. LABELINGN/A
- VII. ESTABLISHMENT INSPECTION.....N/A
- VIII. DRAFT DEFICIENCY LETTER.....N/A



Chemistry Review Data Sheet

1. NDA 21-763
2. REVIEW #: 2
3. REVIEW DATE: December 12, 2005
4. REVIEWER: Lyudmila N. Soldatova, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Review #1

Document Date

07-FEB-05

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

N (AZ) Amendment
N (BZ) Amendment

Document Date

24-JUN-2005
15-NOV-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Biovail Laboratories Incorporated
Chelston Park, Building 1, Ground Floor
Address: Collymore Rock, St. Michael
Barbados, West Indies



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Mr. John Dubeck
Agent for Biovail Laboratories Inc.
Keller and Heckman, LLP
1001 G Street, N.W. Suite 500 West
Washington, D.C. 20001

Telephone: (202) 434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Citalopram Hydrobromide
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Depression

11. DOSAGE FORM: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

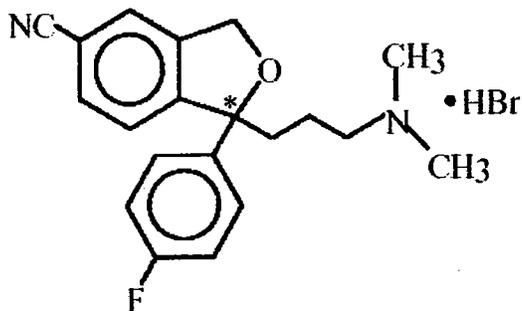
Not a SPOTS product

CHEMISTRY REVIEW

Chemistry Review Data Sheet

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

CA Name: 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)1,3-dihydroisobenzofuran-5-carbonitrile, HBr
USAN Name: 1-[3-(dimethylamino)-propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile mono-hydrobromide
Non-Proprietary Name: Citalopram HBr
Chemical Formula: C₂₀H₂₁FN₂O · HBr
Molecular Weight: 405.30
CAS registry #: 59729-32-7 (Racemate)
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE D	COMMENTS
[REDACTED]	II	[REDACTED]	[REDACTED]	1	Inadequate	26-JUL-2004	Drug Substance
					Inadequate	Dr. David Scanchy	
					Inadequate	10-FEB-2005	
					Adequate	28-NOV-2005	
III	III	[REDACTED]	3	Adequate	25-AUG-2004	July 15, 2003 LOA provided for section 107. Amendment September 02, 2004 answers the	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

						questions raised in the review. Change in the Material Specification number from [redacted] stands for the cosmetic changes to the [redacted]
				1	Adequate	3-NOV-2004, Dr. Lyudmila Soldatova July 15, 2003 LOA provided for section 81. Change in the Material Specification number from [redacted] stands for the cosmetic changes to the [redacted]
	IV			3	Adequate	12-FEB-2004 Dr. Donald Klein Flavorant, February 27, 2004 LoA provided
	IV			1	Adequate	24-JAN-2005 Dr. Lyudmila Soldatova June 3, 2004 LoA provided
	IV			4	Adequate	9-DEC-2004 Dr. Lyudmila Soldatova March 10, 2004 LoA provided
	IV			3	Adequate	06-APR-2001 Dr. J.Salemme 08-FEB-2005 Dr. B.Wu for Eudragit NE40D LoA provided (no date indicated)
	IV			1,4	Adequate	21-APR-1998 Dr. Martha Heimann 9-DEC-2004 Dr. Lyudmila Soldatova February 2, 2004 LoA provided
	IV			3	Adequate	7-MAR-2004 Dr. Donald Klein January 22, 2004 LoA provided

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")



CHEMISTRY REVIEW



Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	07-OCT-05	OC recommendation
Pharm/Tox	No issues statement	23-NOV-05	Linda Fossom, Ph.D.
Biopharm	Acceptable	02-FEB-05	Ta-Chen Wu, Ph.D.
LNC	USAN available	N/A	N/A
Methods Validation	N/A	N/A	Lyudmila Soldatova, Ph.D.
OPDRA	Pending		Trade name is not proposed
EA	Acceptable, categorical exclusion granted as per information from Biovail Inc. in this review	As per this review	Lyudmila Soldatova, Ph.D.
Microbiology	N/A	N/A	N/A

Appears This Way
On Original



The Chemistry Review for NDA 21-763

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Biovail has adequately addressed the CMC deficiencies specified in the Approvable Letter from 2/14/05. NDA 21-763 for Citalopram Hydrobromide ODTs is recommended **APPROVAL** from the CMC standpoint.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Citalopram Hydrobromide Orally Disintegrating Tablets (ODTs) are indicated for the treatment of depression. Citalopram hydrobromide is a selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents.

Citalopram hydrobromide was originally approved under NDA 20-822 (1998), as film-coated tablets (Celexa™ Tablets, 10, 20, 40 and 60 mg) manufactured by Forest Laboratories, New York, NY. The proposed drug product, Citalopram Hydrobromide ODTs, will be marketed in strengths of 10, 20 and 40 mg. No proprietary name was proposed yet for Citalopram ODTs. Drug product will be manufactured in the following manner: the uncoated citalopram hydrobromide, _____ produced by Biovail's proprietary CEFORM™ technology will be coated with an aqueous based, _____

_____ will be combined then with the remaining excipients. The tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, low substituted hydroxypropyl cellulose, croscopovidone, sodium stearyl fumarate, silicon dioxide, citric acid, glyceryl distearate, hypromellose 2910, talc, acesulfame potassium, polyacrylate dispersion 30%, stearyl macrogolglyceride, Tangerine Orange Flavor, Natural Lemon-Lime Flavor, Green Lake Blend, LB-211 and FD&C Yellow No.6. The tablets are round speckled tablets with a dimple on both sides and debossed with "10", "20" or "40" on one side, and the colors are distinct for each strength. On request, Biovail included a unique identifier, i.e. debossed "10", "20" or "40" on one side of the respective tablet, and provided samples of the debossed tablets.

The pivotal commercial-scale batches were manufactured at the proposed commercial manufacturing facilities, Biovail's Dublin, Ireland and Dorado, PR. The primary commercial site for manufacturing, including all packaging operations, is intended to be Dorado, PR. The Dublin, Ireland site is an R&D site and commercial back-up supply only if required. To date Biovail has not shipped any commercial bulk ODTs from Dublin. Biovail committed to conduct shipping/holding time studies and collect stability data (including physical testing results such as friability) to evaluate any effect bulk storage/shipment has on commercial product and its storage, and to submit to the Division, post-approval, prior to any transportation of commercial bulk citalopram ODTs. Detailed information was provided for the manufacturing of the drug product including description of the CEFORM™ technological process (provided on request), for in-process controls and tests for the general process. The equipment used at Biovail's Dublin and Dorado facilities was of different operating classes (defined by SUPAC). Comparative batch analyses for batches produced at these two sites were provided. Release data for batches from two different sites were comparable except for the dissolution data for one Dorado batch (biobatch, 20 mg ODTs), which had lower dissolution values. In response to the request, Biovail explained that this difference was a function of aging of the product and not due to differences in manufacturing or formulation details, and stated that this change is non-biorelevant. This explanation is acceptable based on the OCPB's recommendation to accept the Biovail's proposal to retain the dissolution specification of Q= [redacted] in [redacted] minutes as the interim specifications, and acceptance of the *in vivo* bioequivalence study results. On request, actual disintegration data for release and stability of Citalopram Hydrobromide ODTs 10 mg, 20 mg and 40 mg manufactured at both sites, Dublin and Dorado, were provided by Biovail. Disintegration data demonstrate that ODTs of all three strengths met the specification of NMT [redacted] for all tested conditions through 12 months. The release specifications for ODTs included appearance, identification (HPLC), assay (HPLC), content uniformity (HPLC), impurities (HPLC), dissolution (USP <711> + HPLC), disintegration (USP<701) and moisture content. The release and stability specifications for the drug product are identical except for Identification and Content Uniformity tests, which are absent in the stability specifications. Several deficiencies indicated in the validation of the analytical methods were adequately addressed.

Each strength of Citalopram ODTs is packaged in 6 count [redacted] aluminum foil blisters with child resistant lidding, which will be packaged in cartons. Labeling for blister packages and cartons has been provided by the applicant on request. The 12-month stability data (long-term and intermediate conditions) and 6-month stability data (accelerated condition) were provided for Dublin, Ireland batches, and 6-month stability data (long-term, intermediate and accelerated conditions) for Dorado, PR batches were provided in the original NDA and in the following amendment. Based on the available stability data, a 12-month expiration dating period could be granted for Citalopram ODTs, 10 mg, 20 mg and 40 mg.

The drug substance, citalopram hydrobromide, does not have a monograph in any pharmacopoeia. The same drug substance has been studied in the approved NDA 20-822 for CELEXA™ film-coated tablets in the treatment of depression but it was manufactured by the different supplier [redacted]. For information regarding

chemistry, manufacturing and controls of the citalopram hydrobromide for this NDA 21-763, [REDACTED] DMF # [REDACTED] is cross-referenced. A Letter of Authorization to reference DMF # [REDACTED] dated 09/01/2003 was provided. The drug substance, citalopram hydrobromide, is manufactured by [REDACTED] according to the process and controls described in their DMF # [REDACTED] and supplied to the applicant in a [REDACTED] form. Biovail tested the drug substance according to the Biovail's specifications and does not manipulate it prior to its use in the manufacture of Citalopram hydrobromide ODTs. The DMF [REDACTED] was found adequate by Dr. Lyudmila Soldatova (Review #4 dated 11/28/05). Citalopram hydrobromide is a white to almost white powder; [REDACTED] produced as a racemate. Batch analysis data for four drug substance batches tested by Biovail's Dublin and Dorado facilities (drug product manufacturers) were submitted in the NDA. Deficiencies found in the Biovail's drug substance specifications, were adequately addressed.

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

Citalopram hydrobromide ODTs will be marketed in strengths of 10, 20 and 40 mg in 6 count [REDACTED] aluminum foil blisters with child resistant lidding. Blisters will be packed in cartons. The maximum recommended daily dose is 40 mg/day. Citalopram hydrobromide ODTs will be administered at the initial dose of 20 mg once daily, generally with increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg, at intervals of no less than one week. Doses above 40 mg are not ordinarily recommended. Citalopram ODTs disintegrate in seconds in the mouth; they may be taken with or without food or water, in the morning or evening, and once daily. Please refer to the medical review for any additional information concerning the dosage and administration of Citalopram ODTs. The storage conditions for the drug product are "Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]". The sponsor add a "Protect from light" statement in the How Supplied section of the Package Insert and on the Blister Cartons.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-763 for Citalopram Hydrobromide ODTs is recommended **Approval** from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

ChemistName/Date: Lyudmila Soldatova, Ph.D



ChemistryTeamLeaderName/Date: Thomas Oliver, Ph.D.
ProjectManagerName/Date: Renmeet Gujral, Pharm.D.

B. CC Block

See DFS.

45 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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

/s/

Lyudmila Soldatova
12/14/2005 04:43:57 PM
CHEMIST

Thomas Oliver
12/14/2005 04:48:57 PM
CHEMIST



NDA 21-763

**TradeNameTM (Citalopram Hydrobromide)
Orally Disintegrating Tablets**

Biovail Technologies, Ltd.

Lyudmila N. Soldatova, Ph.D.

***DIVISION OF NEUROPHARMACOLOGICAL DRUG
PRODUCTS***

Review of Chemistry, Manufacturing, and Controls



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b. Characterization / Proof Of Structure	14
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Chemistry Review Data Sheet

1. NDA 21-763
2. REVIEW #: 1
3. REVIEW DATE: October 29, 2004
4. REVIEWER: Lyudmila N. Soldatova, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

14-APR-2004

N(BC) Amendment

05-AUG-2004

N(BC) Amendment

13-AUG-2004

N(BC) Amendment

18-AUG-2004

N(BC) Amendment

23-AUG-2004

N(BC) Amendment

04-OCT-2004

N(BC) Amendment

22-NOV-2004

N(BC) Amendment

13-DEC-2004

N (C) Amendment

13-DEC-2004

N(BC) Amendment

14-DEC-2004

N(BC) Amendment

21-DEC-2004

7. NAME & ADDRESS OF APPLICANT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Name: Biovail Laboratories Incorporated
Address: Chelston Park, Building 1, Ground Floor
Collymore Rock, St. Michael
Barbados, West Indies
Mr. John Dubeck
Agent for Biovail Laboratories Inc.
Representative: Keller and Heckman, LLP
1001 G Street, N.W. Suite 500 West
Washington, D.C. 20001
Telephone: (202) 434-4125

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Citalopram Hydrobromide
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Depression

11. DOSAGE FORM: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

Chemistry Review Data Sheet

_____ SPOTS product – Form Completed

 X Not a SPOTS product

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

CA Name: 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr

USAN Name: 1-[3-(dimethylamino)-propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile monohydrobromide

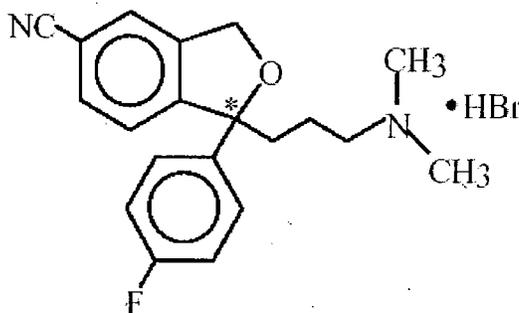
Non-Proprietary Name: Citalopram HBr

Chemical Formula: C₂₀H₂₁FN₂O · HBr

Molecular Weight: 405.30

CAS registry #: 59729-32-7 (Racemate)

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ² .	DATE REVIEW COMPLETE	COMMENTS
1	II	[Redacted]	[Redacted]	1	Inadequate	26-JUL-2004 Dr. David Scanchy	Drug Substance
					Inadequate	FEB-2005 Dr. Lyudmila Soldatova	
3	III			3	Adequate	25-AUG-2004 Dr. Alan Schroeder	July 15, 2003 LOA provided for section 107.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

				Amendment September 02, 2004 answers the questions raised in the review. Change in the Material Specification number from [redacted] stands for the cosmetic changes to the [redacted]	
		1	Adequate	3-NOV-2004, Dr. Lyudmila Soldatova	July 15, 2003 LoA provided for section 81. Change in the Material Specification number from [redacted] stands for the cosmetic changes to the [redacted]
	IV				
		3	Adequate	12-FEB-2004 Dr. Donald Klein	February 27, 2004 LoA provided
		1	Adequate	24-JAN-2005 Dr. Lyudmila Soldatova	June 3, 2004 LoA provided
		4	Adequate	9-DEC-2004 Dr. Lyudmila Soldatova	March 10, 2004 LoA provided
		3	Adequate	06-APR-2001 Dr. J.Salemme	[redacted] LoA provided (no date indicated)
		1,4	Adequate	21-APR-1998 Dr. Martha Heimann 9-DEC-2004 Dr. Lyudmila Soldatova	February 2, 2004 LoA provided
		3	Adequate	7-MAR-2004 Dr. Donald Klein	January 22, 2004 LoA provided

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	31-JAN-05	OC recommendation
Pharm/Tox	Pending		Linda Fossom, Ph.D.
Biopharm	Acceptable	02-FEB-05	Ta-Chen Wu, Ph.D.
LNC	USAN available	NA	NA
Methods Validation	Pending		Lyudmila Soldatova, Ph.D.
OPDRA	Pending		Trade name is not proposed
EA	Acceptable, categorical exclusion granted as per information from Biovail Inc. in this review	As per this review	Lyudmila Soldatova, Ph.D.
Microbiology	NA	N/A	N/A

**Appears This Way
On Original**



The Chemistry Review for NDA 21-763

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-763 for Citalopram Hydrobromide ODTs is recommended **APPROVABLE** from the CMC standpoint. The approval from CMC standpoint is contingent on adequate responses to the CMC deficiencies outlined in this review.

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

None as per this review.

II. Summary of Chemistry Assessments

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

Citalopram Hydrobromide Orally Disintegrating Tablets (ODTs) are indicated for the treatment of depression. Citalopram hydrobromide is a selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents.

Citalopram hydrobromide was originally approved under NDA 20-822 (1998), as film-coated tablets (Celexa™ Tablets, 10, 20, 40 and 60 mg) manufactured by Forest Laboratories, New York, NY. The proposed drug product, Citalopram Hydrobromide ODTs, will be marketed in strengths of 10, 20 and 40 mg. No proprietary name was proposed yet for Citalopram ODTs. The maximum recommended daily dose is 40 mg/day, however, the 60 mg/day dose was investigated but did not result in a superior effect, and, therefore, is not recommended. Drug product will be manufactured in a following manner: the uncoated citalopram hydrobromide [REDACTED] produced by Biovail's proprietary CEFORM™ technology will be coated with an aqueous based [REDACTED]

[REDACTED] will be combined then with the remaining excipients. The tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, low substituted hydroxypropyl cellulose, crospovidone, sodium stearyl fumarate, silicon dioxide, citric acid, glyceryl distearate, hypromellose 2910, talc, acesulfame potassium, polyacrylate dispersion 30%, stearyl macroglyceride, Tangerine Orange Flavor, Natural Lemon-Lime Flavor, Green Lake Blend, LB-211 and FD&C Yellow No.6. Biovail provided copies of the statements from the suppliers of the inactive excipients, stearyl macroglyceride, monoammonium glycyrrhizinate, sodium stearyl fumarate, and



Executive Summary Section

glyceryl distearate, showing that these excipients were derived from vegetable/plant sources but not animal source. The tablets are round speckled tablets with a dimple on both sides, and their colors are distinct for each strength, but each tablet does not have a unique identifier, as noted in the Components/Composition section of the Drug Product and How Supplied section of the Package Insert.

The pivotal commercial-scale batches were manufactured at the proposed commercial manufacturing facilities, Biovail's Dublin, Ireland and Dorado, PR. All packaging operations will be performed at one facility located in Dorado, PR (as per changes reported in the Amendment 10/04/04). As a result, Citalopram ODTs manufactured in Dublin, Ireland will be bulk shipped [REDACTED] to the Dorado, PR site. The batch formulae for the proposed commercial batches of [REDACTED] Citalopram ODTs manufactured at both manufacturing sites are approximately proportional in respect to the unit formulas for all components except for that of the Polyacrylate Dispersion (30%); the applicant was asked to provide the clarification on this issue. Regarding the proportion of the components in the tablets of different strengths, 10 mg tablet has a highest content of the mannitol and a lowest content of the [REDACTED] and the 40 mg tablet has the lowest content of the mannitol and the highest content of the [REDACTED]. Therefore, the 20 mg tablet strength is bracketed in a way regarding the proportionality of the ODT components among all three dosage strengths. Detailed information was provided for the manufacturing of the drug product, however, additional information on the CEFORM™ technological process and on in-process controls and tests for the general process was requested from the applicant. The equipment used at Biovail's Dublin and Dorado facilities was of different operating classes (defined by SUPAC). Comparative batch analyses for batches produced at these two sites were provided. Release data for batches from two different sites were comparable except for the dissolution data for one Dorado batch (biobatch), which had lower dissolution values. Actual disintegration values were not provided for any batch. The release specifications for ODTs included appearance, identification (HPLC), assay (HPLC), content uniformity (HPLC), impurities (HPLC), dissolution (USP <711> + HPLC), disintegration (USP <701>) and moisture content. Dissolution specification and method should be modified according to Biopharm request (see Biopharm review). The release and stability specifications for the drug product are identical except for Identification and Content Uniformity tests, which are absent in the stability specifications. Validated analytical methods were provided in the submission; these methods contained several deficiencies to be addressed to.

Each strength of Citalopram ODTs is packaged in 6 count [REDACTED] aluminum foil blisters with child resistant lidding, which will be packaged in cartons. Labeling for blister packages has not yet been provided by the applicant. The 12-month stability data (long-term and intermediate conditions) and 6-month stability data (accelerated condition) were provided for Dublin, Ireland batches, and 6-month stability data (long-term, intermediate and accelerated conditions) for Dorado, PR batches were provided in the original NDA and December 13, 2004 amendment. Based on this data, the applicant proposed an expiration dating period of 18 months for all strengths of Citalopram Hydrobromide ODTs. The recommended expiry will be determined in Review #2.

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The drug substance, citalopram hydrobromide, does not have a monograph in any pharmacopoeia. The same drug substance has been studied in the approved NDA 20-822 for CELEXA™ film-coated tablets in the treatment of depression but it was manufactured by the different supplier ([REDACTED]). For information regarding chemistry, manufacturing and controls of the citalopram hydrobromide for this NDA 21-763, [REDACTED] DMF # [REDACTED] is cross-referenced. A Letter of Authorization to reference DMF # [REDACTED] dated 09/01/2003 was provided. The drug substance, citalopram hydrobromide, is manufactured by [REDACTED] according to the process and controls described in their DMF # [REDACTED] and supplied to the applicant in a [REDACTED] form. Biovail tested the drug substance according to the Biovail's specifications and does not manipulate it prior to its use in the manufacture of Citalopram hydrobromide ODTs. The DMF # [REDACTED] was originally reviewed by Dr. David Scanchy (Review #1, Inadequate) and, subsequently, by Dr. Lyudmila Soldatova (Review #2, Inadequate). Citalopram hydrobromide is a white to almost white powder; [REDACTED] and produced as a racemate. All batches of citalopram hydrobromide drug substance presented in the original NDA were manufactured at the [REDACTED] plant in [REDACTED]. Batch analysis data for four drug substance batches tested by Biovail's Dublin and Dorado facilities (drug product manufacturers) were submitted in the NDA. Deficiencies were found in the Biovail's drug substance specifications, which are reported in this review.

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

Citalopram hydrobromide ODTs will be marketed in strengths of 10, 20 and 40 mg in 6 count [REDACTED] aluminum foil blisters with child resistant lidding. Blisters will be packed in cartons. The maximum recommended daily dose is 40 mg/day. Citalopram hydrobromide ODTs will be administered at the initial dose of 20 mg once daily, generally with increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg, at intervals of no less than one week. Doses above 40 mg are not ordinarily recommended. Citalopram ODTs disintegrate in seconds in the mouth; they may be taken with or without food or water, in the morning or evening, and once daily. Please refer to the medical review for any additional information concerning the dosage and administration of Citalopram ODTs. The storage conditions for the drug product are "Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]". The sponsor will be asked to add a "Protect from light" statement.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-763 for Citalopram Hydrobromide ODTs is recommended **Approvable** from CMC standpoint based on CMC deficiencies concerning the drug substance and drug product sections as indicated in the review.



III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

ChemistName/Date: Lyudmila Soldatova, Ph.D

ChemistryTeamLeaderName/Date: Thomas Oliver, Ph.D.

ProjectManagerName/Date: Renmeet Gujral, Pharm.D.

B. CC Block

See DFS.

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/s/

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