CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021879Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Office of New Drug Quality Assessment
Division of Neurology Drug Products
Chemistry, Manufacturing, and Controls

DATE: 28-OCT-2010
TO: NDA 21-879
FROM: Thomas Wong, Ph.D., CMC Reviewers, ONDQA/Branch 1
SUBJECT: Final CMC Recommendation for NDA 21-879, Nuedexta™ (dextromethorphan and quinidine) Capsule

Previous Document: Review #2 (in DARRTS) dated 23-JUL-2010

DRUG SUBSTANCE

There were pending deficiencies in the DMF (b) (4) which have been resolved in the current cycle.

Conclusion: Drug substances dextromethorphan and quinidine are satisfactory. There is no outstanding deficiency.

DRUG PRODUCT

The trade name has been changed from Zenvia to Nuedexta.

There was insufficient stability data to assess expiry dating period for the drug products. The applicant provided stability updates in the Amendment #0045 (see review comment below after the Recommendation section). Based on provided stability data, a **24 months expiration dating period is granted for DM 20 mg/Q 10 mg** (b) (4) **capsules** when packaged in the proposed commercial packages and stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Conclusion: Drug product is satisfactory. There is no outstanding deficiency.

EES

The Office of Compliance has issued a final overall recommendation of acceptable on Oct 28, 2010 (see attached EES summary report).

Conclusion: EES status is acceptable.

Recommendation: From a CMC perspective, the application is recommended for Approval.

Review of updated stability data provided in Amendment #0045:

In the amendment #0045, the applicant updated the long term stability results by providing 36 months data for one batch (b) (4) capsules in 60 counts bottle and up to 12 months for two batches (b) (4) capsules in 13, 60 (b) (4) counts. The proposed commercial packaging is 60 counts per bottle and the 13 counts per bottle packaging is physician sample. (b) (4) Following is the summary of the updates:

DM 20 mg/Q 10 mg Capsules

Bulk Batch #	Packaging Batch #	Packaging Configuration	Stability Data
PD284M-001	PD284-001	60 Capsules	From 24 to 36 Months
	C9G24171	13 Capsules	From 6 to 12 Months
C9G2082	C9G20821	60 Capsules	From 6 to 12 Months
	C9G20822	13 Capsules	From 6 to 12 Months
	(b) (4)		
C9G2083	C9G20831	60 Capsules	From 6 to 12 Months
	C9G20832	13 Capsules	From 6 to 12 Months
	(b) (4)		

(b) (4)

The applicant provided the following trend analysis in the amendment.

Stability Trend Analysis for Assay of Dextromethorphan in Zenvia
20/10 (b) (4) lots in 13 and 60-counts Bottles Stored at 25°C/60% RH

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(b) (4)

Evaluation: (b) (4)

the product is stable at least up to 24 months and support the 24 months expiry period. The available data, however, is insufficient to support the applicant's proposed expiry dating period of (b) (4) months.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21879/000	**Sponsor:**	AVANIR PHARMS
Org. Code:	120		101 ENTERPRISE STE 300
Priority:	4P		ALISO VIEJO, CA 92656
Stamp Date:	30-JAN-2006	**Brand Name:**	NEURODEX(DEXTROMETHORPHAN PLUS QUINIDINE
PDUFA Date:	30-OCT-2010	**Estab. Name:**	
Action Goal:		**Generic Name:**	DEXTROMETHORPHAN PLUS QUINIDINE
District Goal:	31-AUG-2010	**Product Number; Dosage Form; Ingredient; Strengths**	

(b) (4)

002; CAPSULE, HARD GELATIN; DEXTROMETHORPHAN HYDROBROMIDE; 20MG
002; CAPSULE, HARD GELATIN; QUINIDINE SULFATE; 10MG

FDA Contacts:	D. HENRY	Project Manager		301-796-4227
	T. WONG	Review Chemist	(HFD-810)	301-796-1608
	M. HEIMANN	Team Leader		301-796-1678

Overall Recommendation:	ACCEPTABLE	on 28-OCT-2010	by E. JOHNSON	(HFD-320)	301-796-3334
	ACCEPTABLE	on 15-JUL-2008	by ADAMSS		
	ACCEPTABLE	on 01-JUN-2006	by ADAMSS		

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAY-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-MAY-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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/s/

THOMAS M WONG
10/28/2010

RAMESH K SOOD
10/28/2010

NDA 21-879

Zenvia™ Capsules
(Dextromethorphan Hydrobromide plus Quinidine Sulfate)

Avanir Pharmaceutical

Thomas M. Wong, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Division of Neurology Drug Products
Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-879

2. REVIEW #: 2 (Review #1 was for Neurodex™ Capsule - (b) (4) This review is for Zenvia™ Capsules - (b) (4) DM 20 mg/Q 10 mg)

3. REVIEW DATE: August 11, 2010

4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA CMC submission	9-MAR-2005
Amendment C	26-SEP-2005
Amendment BC	18-OCT-2005
Amendment BL	3-FEB-2006
Amendment BC	28-FEB-2006
Amendment C	20-MAR-2006
Amendment BZ	23-MAR-2006
Amendment BZ	26-APR-2006
Amendment BZ	4-MAY-2006
Amendment (by email)	30-MAY-2006
Chemistry Review #1 (Reviewer Dr. G. Gill-Sangha)	21-JUN-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Re-submission #0035	23-APR-2010
Amendment 0040	20-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Avanir Pharmaceuticals

Address: 101 Enterprise, Suite 300
Alison Viejo, CA 92656

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zenvia™
b) Non-Proprietary Name (USAN): Dextromethorphan Hydrobromide [DM] USP and Quinidine Sulfate [Q] USP
c) Code Name/#: AVP-923
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Treatment of Psuedobulbar Affect (PBA)

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: (b) (4) DM 20 mg/Q 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

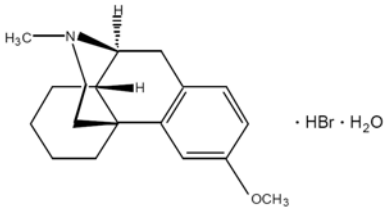
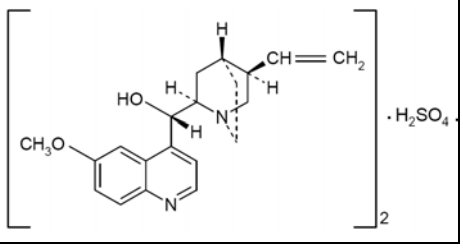
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

USAN Name:	Dextromethorphan Hydrobromide	Quinidine Sulfate
CAS Name:	Morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α)-,hydrobromide monohydrate	Cinchonan-9-ol, 6'-methoxy-, (9 S) sulfate (2:1), (salt), dihydrate
CAS registry #:	6700-34-1	6591-63-5
Company code:	NA	NA
Molecular	370.33	782.96

weight:		
Molecular formula:	$C_{18}H_{25}NO•HBr•H_2O$	$(C_{20}H_{24}N_2O_2)_2 . H_2SO_4 . 2H_2O$
Structure:		

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	7	Inadequate		Deficiencies responses are being reviewed
	II			1	Adequate	July 9, 2010	Review #11
	IV			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application
	III			4			Sufficient information in application

[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")

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		Office of Compliance
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMFPA	N/A		
EA	Acceptable/categorical exclusion	As per this review	Thomas M. Wong, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-879

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-879 for Zenvia™ Capsules (Dextromethorphan Hydrobromide plus Quinidine Sulfate) **CANNOT BE APPROVED** from the CMC standpoint due to the following pending issues:

1. There are deficiencies in the DMF (b) (4) which have not yet been resolved.
2. The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.

The expiry date has not been recommended due to insufficient stability data in the re-submission filing. The applicant was requested to provide additional stability data for assessment of expiry dating period for the products. The applicant responded that additional stability data will be submitted early September, 2010. Expiry dating period for the products will be assessed after the review of the additional stability data.

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

None at this time.

II. Summary of Chemistry Assessments

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

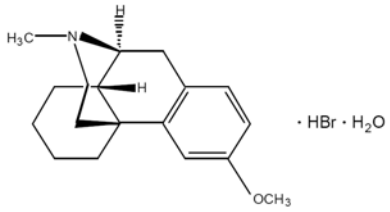
Introduction

Zenvia capsules contain a combination of two active ingredients - dextromethorphan hydrobromide (DM) and quinidine sulfate (Q)

Drug Substance

Dextromethorphan hydrobromide (DM), USP:

One of the drug substances for Zenvia capsules is dextromethorphan hydrobromide (DM) chemically known as Morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α)-,hydrobromide monohydrate. Its molecular formula is $C_{18}H_{25}NO \bullet HBr \bullet H_2O$ and its molecular weight is 370.33. The structural formula for DM is:

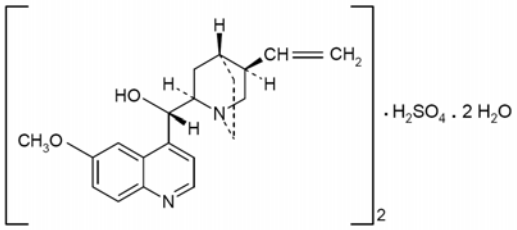


The solubility of dextromethorphan hydrobromide in water is 1.5 g/100 mL, in ethanol is 25 g/100 mL, and is freely soluble in chloroform, and practically insoluble in ether. Dextromethorphan hydrobromide has not been shown to exhibit polymorphism.

Detailed information of the drug substance can be found in DMF # (b) (4) which is being reviewed by Dr. Bahar Zarabi.

Quinidine sulfate (Q), USP:

The other drug substance for Zenvia capsules is quinidine sulfate (Q) chemically known as Cinchonan-9-ol, 6'-methoxy-, (9 S) sulfate (2:1), (salt), dihydrate**.** Its molecular formula is $(C_{20}H_{24}N_2O_2)_2 . H_2SO_4 . 2H_2O$ and its molecular weight is782.96. The structural formula for Q is:



The solubility of quinidine sulfate in water is 1g/90 mL, in ethanol is 1g/10 mL, is insoluble in ether and benzene. Quinidine sulfate has not been shown to exhibit polymorphism.

Detailed information of the drug substance can be found in DMF # (b) (4) which has been reviewed by Dr. Gurpreet Gill-Sangha on March 27, 2006 and found to be adequate.

Drug Product

Zenvia capsule is an immediate release capsule containing a combination of two active ingredients - dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) and is indicated for the treatment of psuedobulbar affect (PBA). The capsules are available in (b) (4) 20mg/10 mg on an anhydrous basis, with the following description:

- DM 20 mg/Q 10 mg capsule: size 1opaque Swedish orange (brick-red) color capsule with printing of "DMQ/20-10" in white ink on the cap and unprinted body.

(b) (4)

The capsules contain dextromethorphan hydrobromide and quinidine sulfate active ingredients with the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, colloidal silicon dioxide, lactose monohydrate, and magnesium stearate. The manufacturing process (b) (4)

The capsules will be packaged and marketed as 60 counts in white HDPE bottles with child resistant closure with foil induction seal. The capsules will also be packaged as 13 counts in white HDPE bottles with child resistant closure with foil induction seal as physician samples.

The expiry date has not been recommended due to insufficient stability data in the re-submission filing. The applicant was requested to provide additional stability data for assessment of expiry dating period for the products. The applicant responded that additional stability data will be submitted early September, 2010. Expiry dating period for the products will be assessed after the review of the additional stability data.

Additional Items

DMFs: All associated Drug Master Files except (b) (4) are acceptable or the pertinent information has been adequately provided in the application.

Methods Validation: The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

EES: As of August 11, 2010, the Office of Compliance has not yet provided an overall acceptable recommendation for the manufacturing sites.

Post-Approval Agreements: None.

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

Zenvia capsule is a combination product containing dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) available in (b) (4) 20mg/10 mg on an anhydrous basis and is indicated for the treatment of psuedobulbar affect (PBA). The recommended starting dose is one Zenvia DM 20 mg/Q 10 mg capsule (b) (4) administered daily by mouth for the initial seven days of therapy to be taken with or without food. On the eighth day of therapy and thereafter, the daily dose should be increased by taking a second capsule of Zenvia 20/10 (b) (4) by mouth approximately 12 hours after taking the first dose.

The capsules are to be packaged in white HDPE bottles in 60-count per bottle as commercial presentation and in 13-count per bottle as physicians sample. The products are to be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Avanir Pharmaceuticals, Inc. has submitted sufficient and appropriate information to support the approval of the drug product, Zenvia™ (dextromethorphan hydrobromide and quinidine sulfate) capsules.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Thomas M. Wong, Ph.D.

Branch Chief Name: Ramesh Sood, Ph.D.
Project Manager Name:

C. CC Block

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21879	ORIG-1	AVANIR PHARMACEUTICALS INC	NEURODEX(DEXTROMETHORPHAN PLUS QUINIDINE

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/s/

THOMAS M WONG
08/12/2010
Drug substances DMFs # (b) (4)

RAMESH K SOOD
08/12/2010

NDA 21-879

Neurodex™ Capsules
(Dextromethorphan Hydrobromide plus Quinidine Sulfate)

Avanir Pharmaceutical

Gurpreet Gill-Sangha, Ph.D.
OFFICE OF NEW DRUG QUALITY ASSESSMENT (ONDQA)
Review of Chemistry, Manufacturing, and Controls

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/s/

Gurpreet Gill-Sangha
6/21/2006 01:53:21 PM
CHEMIST

CMC Review #1 for NDA 21-879

Ramesh Sood
6/23/2006 02:48:42 PM
CHEMIST
The expiration date will be revisited if company submits additional stability data prior to action.