CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021879Orig1s000

CHEMISTRY REVIEW(S)
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 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 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 capsules in 60 counts bottle and up to 12 months for two batches capsules in 13, 60 counts. The proposed commercial packaging is 60 counts per bottle and the 13 counts per bottle packaging is physician sample.

Following is the summary of the updates:

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<tr>
<th>Bulk Batch #</th>
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The applicant provided the following trend analysis in the amendment.

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

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
Evaluation:

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 24 months.
Application: NDA 21879/600
Org. Code: 120
Priority: 4P
Stamp Date: 30-JAN-2006
PDUFA Date: 30-OCT-2010
Action Goal: 31-AUG-2010

Sponsor: AVANIR PHARMS
Brand Name: NEURODEX/DEXTROMETHORPHAN PLUS QUINIDINE
Estab. Name: DEXTROMETHORPHAN PLUS QUINIDINE

Product Number; Dosage Form; Ingredient; Strengths:
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:

DMF No: AADA:
Responsibilities: OAI Status: NONE
Profile: OC RECOMMENDATION
Last Milestone: 28-OCT-2010
Milestone Date: ACCEPTABLE
Decision: DISTRICT RECOMMENDATION
Reason:
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: 

DMF No: 

Responsibilities: 

Profile: 

OC RECOMMENDATION

Last Milestone: 

Milestone Date: 

Decision: 

Reason: 

Based on Profile

(b)(4)

(b)(4)

(b)(4)

October 28, 2010 10:30 AM

FDA Confidential - Internal Distribution Only

Page 2 of 2
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/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
# CHEMISTRY REVIEW

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1. NDA 21-879

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

3. REVIEW DATE: August 11, 2010

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

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<td>20-JUL-2010</td>
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7. NAME & ADDRESS OF APPLICANT:

Name: Avanir Pharmaceuticals

Address: 101 Enterprise, Suite 300
          Alison Viejo, CA 92656
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: DM 20 mg/Q 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___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:

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

weight:

Molecular formula: \( \text{C}_{18}\text{H}_{25}\text{NO}\cdot\text{HBr}\cdot\text{H}_{2}\text{O} \)

\( \text{(C}_{20}\text{H}_{24}\text{N}_{2}\text{O}_{2})_{2}\cdot\text{H}_{2}\text{SO}_{4}\cdot\text{2H}_{2}\text{O} \)

Structure:

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\(^{1}\) 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")
Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

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<td>Microbiology</td>
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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 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•HBr•H_{2}O 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] 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 \((C_{20}H_{24}N_{2}O_{2})_2 \cdot H_2SO_4 \cdot 2H_2O\) and its molecular weight is 782.96. The structural formula for Q is:

![Quinidine sulfate structure](image)

The solubility of quinidine sulfate in water is 1 g/90 mL, in ethanol is 1 g/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] 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 20mg/10 mg on an anhydrous basis, with the following description:

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

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...

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 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 20mg/10 mg on an anhydrous basis and is indicated for the treatment of pseudobulbar affect (PBA). The recommended starting dose is one Zenvia DM 20 mg/Q 10 mg capsule 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 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.
Executive Summary Section

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

C. CC Block
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<td>NEURODEX (DEXTROMETHORPHAN PLUS QUINIDINE)</td>
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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.