CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-875

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: February 28, 2007

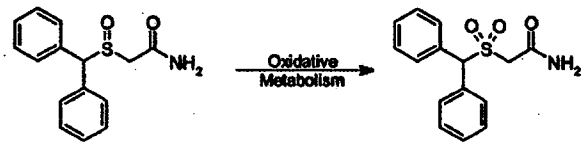
TO: NDA 21-875

FROM: David J. Claffey, PhD

THROUGH: Ramesh Sood, PhD

SUBJECT: **Suspected link of modafinil sulfone to the sulfa class of antibiotics**
NDA 21-875, NUVIGIL (armodafinil) Tablets

Background: On 23 MAR 2006 the Division of Psychiatric Products convened a Psychiatric Drug Advisory Committee meeting to discuss the safety and efficacy of modafinil tablets for the treatment of children with ADHD. This was in response to an efficacy supplement (S-019) to NDA 20-717. The committee recommended not approving this application on a vote of 12:1 based primarily on a single suspected case report of Sevens Johnsons Syndrome (SJS) in a juvenile subject. The discussion during this meeting centered around the possibility that children may react differently than adults to modafinil, as this drug had been marketed under the name Provigil for treatment of certain sleep disorders in adults for many years without an SJS warning in its labeling (although reference is made to rare reports of suspected cases of SJS). Note that this supplement proposes a different brand name "Sparlon" for the proposed ADHD indication. One known difference is that the pharmacokinetics of one of modafinil's metabolites, modafinil sulfone, appeared to be significantly different in children.



Modafinil Modafinil-sulfone

As this metabolite contained a sulfone and an amide group it was inferred during the meeting that this metabolite was a sulfonamide and that it could therefore carry similar risks of severe allergic skin reactions (including SJS) as the sulfonamide or sulfa class of antibiotics. This suspicion along with the single possible case of SJS contributed to the non-approval recommendation from the committee and the subsequent not approvable action letter of 9 AUG 2006 for NDA 20-717/S-019. This issue was also raised in the approvable action letter for NDA

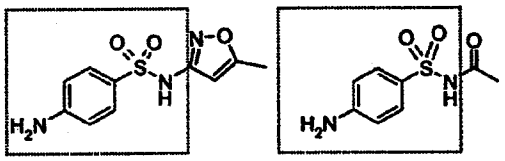
21-875, which provided for the marketing of Nuvigil (armodafinil tablets), the single enantiomeric form of modafinil.

19 DEC 2007 Amendment to NDA 21-875: The applicant responded this presumed link between modafinil sulfone and sulfa drugs in the 19 DEC 2007 amendment to NDA 21-875. This reviewer was asked to evaluate the response. In an email to the review team and at a later multi-Divisional meeting (27 FEB 2007), I concurred with the Applicants determination that modafinil sulfone does not have the structural similarities to the sulfonamide drugs that are known to cause cutaneous reactions for the following reasons:

1. Firstly, sulfa drugs contain a single sulfonamide (SO_2NH_2 or SO_2NHR) functional group. Modafinil sulfone happens to contain separate sulfonyl (SO_2) and carboxyamide ($CONH_2$) groups, so it can be regarded as a 'sulfonyl amide', not a sulfonamide.

2. Secondly, most sulfa drugs contain an aromatic amino group which is capable of reacting with proteins to form haptens, which can initiate allergic reactions. Modafinil sulfone does not have an equivalent reactive group.

The following are examples of the sulfonamide (sulfa) class of antibiotics:



Sulfamethoxazole (an aniline)

Sulfacetamide (component of blephamide)

This reviewer is not dismissing the possible involvement of modafinil sulfone in inducing allergic reactions, however this metabolite does not contain the structural features that are required for sulfa drugs to exert their toxicity *i.e.* the sulfonamide and aromatic amine functional groups.

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

/s/

David Claffey
3/2/2007 07:37:40 PM
CHEMIST

Ramesh Sood
3/5/2007 03:10:00 PM
CHEMIST

NDA 21-875

NUVIGIL (armodafinil) Tablets

Cephalon, Inc.

David J Claffey, PhD

Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-875

2. REVIEW #: 1

3. REVIEW DATE: 6 FEB 2005

4. REVIEWER: David J. Claffey, PhD.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	31 MAR 2005
Amendment (BC)	27 SEP 2205
Amendment (BZ)	25-JAN-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Cephalon, Inc
Address:	145 Brandywine Parkway West Chester, PA 19380
Representative:	Paul M. Kirsch
Telephone:	(610) 738 6122

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NUVIGIL
b) Non-Proprietary Name (USAN): Armodafinil
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 (single enantiomer of previously approved racemate)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) 1

10. PHARMACOL. CATEGORY: Treatment of Excessive Sleepiness with Obstructive Sleep Apnea/Hypopnea Syndrome, Narcolepsy and Shift Work Sleep Disorder.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 50, 100, 150 and 250 mg/tablet

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

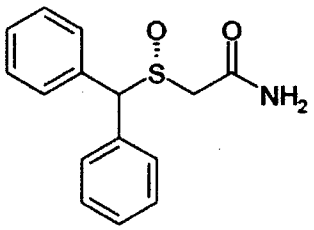
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Compound Name: Armodafinil

Chemical Names: 2-[(R)-(diphenylmethyul)sulfinyl]acetamide

Chemistry Review Data Sheet

Laboratory Codes: CEP-10953; CRL-40982
Levo-modafinil
(-)-modafinil isomer
l-modafinil
R-modafinil

CAS: 112111-43-0



Molecular formula : **$C_{15}H_{15}NO_2S$**

Molecular weight : **273.35**

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate (David J. Claffey)	8 MAR 2006	
					Adequate (David J. Claffey)	8 MAR 2006	

b(4)

Chemistry Review Data Sheet

b(4)

[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
IND	68,517	CEP-10952 (armodafinil)
NDA	20-717	Provigil

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	Acceptable	14-DEC-2005	S. Adams
Microbiology			

19. ORDER OF REVIEW (OGD Only) N/A

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-875

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Recommend Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The proposed drug product is essentially identical in composition to the marketed drug, Provigil (20-717), the main difference being that it contains an [redacted] drug substance, whereas Provigil contains the corresponding racemate. It consists of uncoated [redacted] oral tablets of four strengths (50, 100, 150 and 250 mg). They are white to off-white in **color, debossed with a Cephalon "C" on one** side and a number unique to each strength on the other. The 50 mg and 100 mg are round in shape and the 150 mg and 250 mg are oval-shaped. [redacted] The container closure system for armodafinil tablets (60-count) consists of [redacted] bottles with child-resistant closures and an [redacted] The bottles contain a [redacted] The [redacted] bottles [redacted] used for the proposed armodafinil product are the same as those currently used for Provigil tablets.
The drug substance, armodafinil, is the R-enantiomer of modafinil the drug substance in Provigil (NDA 20-717). [redacted]

b(4)

b(4)

[redacted] The known aqueous insolubility of armodafinil (~1 mg/ml) led to *in vitro*

studies that established a correlation between the rate of armodafinil dissolution in the drug product and its particle size: [redacted]

[redacted] b(4)

Initially a 50 mg armodafinil capsule was developed for Phase I clinical studies. For the pivotal clinical studies 50 mg and 100 mg strength round white film-coated tablets were developed. The tablets were of similar composition to the capsules and of identical composition to both commercial Provigil and the proposed Nuvigil tablets. The only exception is that the clinical tablet lots were film-coated for blinding purposes. For commercial purposes two additional strengths were developed, 150 mg and 250 mg, in the form of oval shaped tablets. The comparability of the clinical tablets with the proposed commercial tablets was established by side-by-side *in vitro* dissolution studies as well as an *in vivo* bioavailability study. Stability data to-date support the proposed [redacted] date for the drug substance and the proposed 24 month expiry period for the drug product. b(4)

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

It is proposed to market the drug product in 60-count bottles [redacted] The recommended dose is 150 or 150 mg given once a day for patients with obstructive sleep apniea/hypopnea syndrome (OSAHS) or narcolepsy, and 150 mg/day for patients with shift work sleep disorder (SWSD). For patients with OSAHS or narcolepsy, Nuvigil should be taken as a single dose in the morning. For patients with SWSD it should be taken approximately one hour prior to the start of their work shift. The current package insert states that in [redacted] b(4)

C. Basis for Approvability or Not-Approval Recommendation

The approval recommendation for this application is based on the following:

- Adequate CMC information for the drug substance in this application and the cross referenced DMFs for the drug substance manufacture (DMF [redacted] and [redacted]
- Adequate CMC information for the drug product (batch formula, controls and analytical test results, containers) and their comparability to the approved Provigil. b(4)
- Stability data that supports the proposed drug product 24 months expiry period
- Acceptable cGMP status for all the manufacturing and testing facilities.

III. Administrative

A. Reviewer's Signature

Electronic (DFS)

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryBranchChiefName/Date
ProjectManagerName/Date

C. CC Block See DFS

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

David Claffey
3/9/2006 10:02:35 AM
CHEMIST

Ramesh Sood
3/9/2006 10:32:31 AM
CHEMIST

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