CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-360

CHEMISTRY REVIEW(S)

NDA 21-360

Sustiva tablets

Bristol-Myers-Squibb

Dan Boring
Division of Antiviral Drug Products
HFD-530

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WITHHOLD 1 PAGE (S)

Chemistry Review Data Sheet

1. NDA 21-360

2. REVIEW #: 1

3. REVIEW DATE: 12/21/01

4. REVIEWER: Dan Boring

5. **PREVIOUS DOCUMENTS: N/A**

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	3/30/2001 {date}
Amendment (BC)	9/28/2001 {date}

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Bristol Myers Squibb
Address:	DuPont Merck Plaza Centre Road Wilmington, DE 19805
Representative:	Chris Vogel
Telephone:	(609) 818-6353

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Sustiva tablets
b) Non-Proprietary Name (USAN): efavirenz
c) Code Name/#: DMP 266
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 300 and 600 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

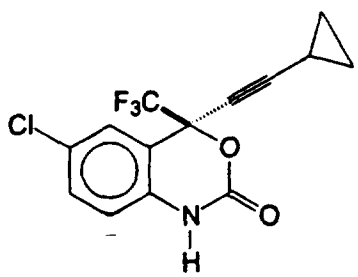
__X___Not a SPOTS product

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

(S)-6-Chloro-4-(cyclopropylethynyl)- 1,4-dihydro-(trifluoromethyl)-2H-3,1-benzoxazin-2-one

$C_{14}H_9ClF_3NO_2$

315.67



APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF#	Holder	DMF Type	Item Ref.	Code[1]	Status[2]	Date Review Completed	Comment
[redacted]	[redacted]	II	[redacted]	3	Adequate		
[redacted]	[redacted]	III	[redacted]	3	Adequate		
[redacted]	[redacted]	III	[redacted]	3, 4	Adequate		
[redacted]	[redacted]	III	[redacted]	3	Adequate		
[redacted]	[redacted]	III	[redacted]	3, 4	Adequate		
[redacted]	[redacted]	III	[redacted]	3	Adequate		

[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
NDA	20-972	Sustiva capsules
IND	[redacted]	Sustiva capsules

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	8/27/01	N/A
OPDRA	Acceptable	12/5/01	Carol Holquist, R.Ph.
EA	Categorical exclusion	N/A	N/A

The Chemistry Review for NDA 21-360

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for 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 and Drug Substance

The chemistry, manufacturing and controls information regarding the drug substance is cross-referenced to the approved NDA 20-972 for Sustiva capsules.

The drug product is an oral, film-coated ——— tablet containing 300 or 600 mg. of efavirenz. The tablet is marked with SUSTIVA on one side. All excipients are compendial except the coating colorants and marking inks. There are no toxicity concerns with the excipients at the exposure level used in the tablets. Early formulation work identified ——— as a critical component for achieving AUC and Cmax comparable to the approved capsule and the amount of ——— during development. The tablet will be manufactured at the DuPont (now BMS) manufacturing facility in Garden City, New York with ——— as an alternate packager and labeler.

The manufacturing process is divided into ——— operations to prepare the tablet by a ——— process. The core tablets for the 300 mg and 600 mg strengths are prepared from ——— of the same composition, and the core tablet weight is adjusted to obtain the appropriate dose. There is no reprocessing done with the tablets. The formulation and manufacturing process of the two tablets are identical to the point of ——— Adequate in-process controls are in place to assure tablet quality. The tablets are packaged in 30 ——— count HDPE bottle presentations and 100-count blister presentations. The blisters are intended for institutional use only.

The tablet specifications include description, identification ——— dissolution, uniformity of dosage units, assay, and degradation products (specified, unknown and total). No microbial growth has ever been observed in the drug substance, approved

capsules or tablets, therefore no microbial testing is being proposed. Likewise, no chiral inversion has been observed in efavirenz tablets on stability through six months at 40C/75%RH. Additionally, no chiral inversion has been seen in the Sustiva capsule after storage for 36 months at 25C/60%RH. Therefore, no chiral testing is proposed. Also, available data indicate that moisture level in the tablets has no impact on physical, chemical, or dissolution attributes. Moisture levels of efavirenz tablets are being monitored on stability, but no specification for moisture in tablets was established. The proposed acceptance criteria for the specification parameters adequately reflects the toxicology qualification limits, product release ranges and stability information.

The bottle and blister presentations of the product provide adequate protection of the product and the materials are satisfactory from a regulatory perspective. There are no significant differences in the behavior of the tablets in either the bottle or blister except that the blister permits more moisture to enter the tablets. There is no stability impact from this additional moisture. After the tablets for the primary stability studies were packaged, the sponsor initiated a transition to a new — cc bottle design allowing for greater labeling surface. The — cc bottle was re-designed, without changing any critical dimensions, to increase the labeling area. The internal volume of the bottle was not changed. This modified bottle has been demonstrated equivalent. This modified — -cc bottle will be used for the 300-mg and 600-mg tablet validation batches and is intended for commercial product use. There is no change to the CR cap or induction seal from the primary stability bottle.

The sponsor provided 6 months of stability information in the original application with an update at 12-months (by Amendment) of primary stability data at 25C/60%RH on 3 lots each of the 300 and 600-mg tablet packaged in both the HDPE bottle and — blister. Additionally, 12 and 18 months of supportive stability data on 2 lots of 600-mg tablets prepared using ——— and ——— was submitted. Also, up to 24 months of supportive data on 1 lot of 300-mg tablets prepared using ———, and ——— was submitted. A statistical analysis of the dissolution and assay was also provided in the same amendment. No statistical analysis of degradants was undertaken because all degradation products were always below — over time for tablets stored in HDPE or film/foil blisters at all storage conditions and there was no trend to analyze

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

The recommended oral dose for efavirenz is 600 mg once daily at bedtime. The efavirenz 300 and 600-mg tablets are a new higher dose intended to make dosing more convenient than the existing capsules (50, 100 and 200-mg) strengths by reducing the pill burden on HIV patients.

The proposed expiration dating of — months is fully supported by the primary and secondary real-time stability information and statistical extrapolation of the real-time data. It is recommended for storage under controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendment ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Sustiva (efavirenz) Tablets.

As amended, all methods and acceptance criteria were found acceptable for the drug product.

The trade name was found acceptable by OPDRA and by the Division of Antiviral Drug Products. There are several labeling recommendations made by OPDRA and the reviewer that will be incorporated by the applicant at the time of the next label printing.

III. Administrative

A. Reviewer's Signature

Signed electronically in DFS

B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

C. CC Block

cc:

Org. NDA 21-360	HFD-530/Chem Reviewer/DBoring
HFD-530/Division File	HFD-530//Chem Team Leader/SMiller
HFD-830/DD/CChen	HFD-530/PM/VYoerg

APPEARS THIS WAY
ON ORIGINAL