CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-128

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-128

From: Donna F. Christner, Ph.D.; Steve Miller, Ph.D.; Sharmista Chatterjee, Ph.D.

Date: 02-Aug-2007

Re: CMC label review of container label and PI from Complete Response

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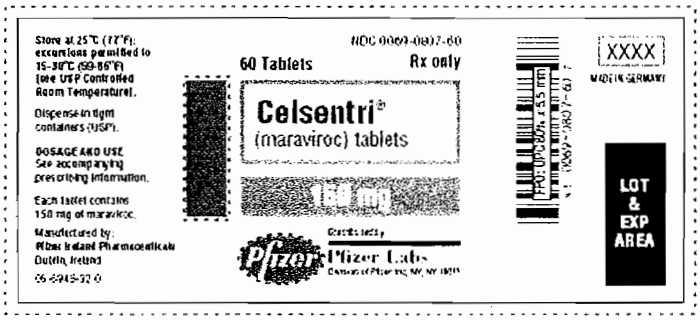
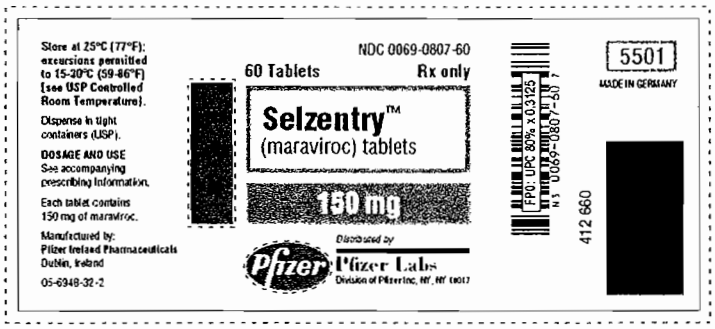
When CMC Review #1 was finalized on 15-Jun-2007, the Tradename was not agreed to. CMC recommended APPROVAL and stated "...Pfizer has been advised that revised bottle, [redacted] and carton labels would be acceptable for commercial use provided the new proprietary name is added using the same font and layout as were submitted with the NDA." The label provided in the NDA is as follows:



The label provided in the Complete Response is as follows:



In addition, the PI remains the same as that in the first review. The sponsor has complied with the request. Response is adequate. The application can be approved from the CMC standpoint.

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

/s/

Donna Christner
8/2/2007 05:30:13 PM
CHEMIST

Memo on container labels

Sharmista Chatterjee
8/2/2007 05:43:59 PM
CHEMIST

Stephen Paul Miller
8/3/2007 10:54:08 AM
CHEMIST

Elaine Morefield
8/3/2007 11:21:06 AM
CHEMIST
The CMC recommendation remains approval.

NDA 22-128

Tradename (maraviroc) Tablets

Pfizer

Donna Christner, Ph.D.
Sharmista Chatterjee, Ph.D.
Stephen Miller, Ph.D.

CMC Review Team

Office of New Drug Quality Assessment
for
Division of Antiviral Products

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-128

2. REVIEW #: 1

3. REVIEW DATE: 15-Jun-2007

4. REVIEWERS: Donna Christner, Ph.D.;
Sharmista Chatterjee, Ph.D.;
Stephen Miller, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission 000	19-Dec-2006
Presubmission 001 (PD Section)	21-Nov-2006
Amendment 038 (Labeling)	23-Mar-2007
Amendment 045 (Responses to 1st IR Letter)	19-Apr-2007
Amendment 066 (Response to 2nd IR Letter)	01-Jun-2007
Amendment 067 (Labeling)	01-Jun-2007
Response to 3rd IR letter (email)	13-Jun-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer Global Research & Development
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Representative: Leilani V. Kapili
Telephone: 860-732-9967

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename
b) Non-Proprietary Name: Maraviroc
c) Code Name/# (ONDC only): UK-427,857
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

CMC Review Data Sheet

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

10. PHARMACOL. CATEGORY: Antiviral (HIV), CCR5 Inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg, 300 mg

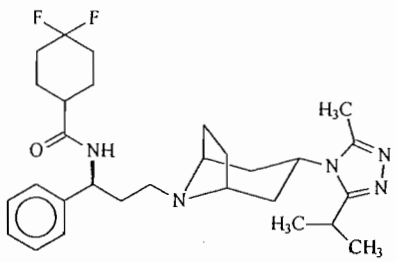
13. ROUTE OF ADMINISTRATION: Oral

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:



Maraviroc

Chemical Names

IUPAC: 4,4-difluoro-N-{(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide

CAS: 4,4-difluoro-N-[(1S)-3-[(3-exo)-3-[3-methyl-5-(1-methylethyl)-4H-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl]-cyclohexanecarboxamide

Molecular Formula: $C_{29}H_{41}F_2N_5O$

Molecular Weight: 513.67 Daltons

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			1	Adequate	10-May-2007	
	III			3	Adequate	12-Jan-2005	Adequate for NDA 50-795 by R. Madurawe
	III			3	Adequate	22-Jul-2005	Adequate for NDA [redacted] by C. Bertha
	III			3	Adequate	22-Jun-2006	Adequate for NDA 21-991 by J. Jee
	III			1	Adequate	10-May-2007	
	III			3	Adequate	11-Mar-2005	Adequate for NDA 21-266 by G. Holbert
	III			3	Adequate	07-Mar-2003	Adequate for NDA 21-549 by J. Salemme
				3	Adequate	02-Sep-2003	Adequate for NDA 21-621 by E. Jao
	III			3	Adequate	27-Feb-2001	DMF Strike Force
	III			3	Adequate	27-Feb-2004	Adequate for NDA 7-337 by D. Chiapperino
				3	Adequate	19-May-2003	Adequate for NDA [redacted] by D. Klein
	III			3	Adequate	23-Jun-2006	Adequate for NDA 21-991 by J. Jee
				7	N/A	N/A	Not a CMC related DMF

CMC Review Data Sheet

[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	65,229	
NDA		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	11-Jun-2007	S. Adams
Pharm/Tox	N/A		
Biopharm			
LNC	N/A		
Method Validation	N/A, according to the current ONDC policy		
DMETS	Final recommendation pending	15-Jun-2007	
EA	Categorical exclusion granted	11-Jun-2007	CMC Review Team
Microbiology	N/A		

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The CMC Review for NDA 22-128

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA was reviewed as part of the Pharmaceutical Quality Assessment System (PQAS) Pilot Program, and as amended it is recommended for approval from the CMC perspective. Questions and recommendations from the CMC review team were sent to Pfizer in information request letters on March 29, May 24 and June 11, 2007. Pfizer's responses were judged to be adequate, and all critical CMC issues related to approvability were resolved satisfactorily. Topics related to the PQAS Pilot Program are discussed in greater detail in Section II C, below.

The information provided in the NDA supports the approval of the 150 and 300 mg tablets, packaged in [redacted] bottles [redacted] 60-count) [redacted] . An expiration dating period of 24 months, when stored at 25°C [USP Controlled Room Temperature] is supported by the available stability data. While all these packaging configurations are approved [redacted] Because of uncertainties about the proposed proprietary name, from the medication errors perspective, Pfizer has been advised that revised bottle, [redacted] and carton labels would be acceptable for commercial use provided the new proprietary name is added using the same font and layout as were submitted with the NDA.

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

None

II. Summary of CMC Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Maraviroc drug substance is a stable crystalline material produced by synthesis. It has high solubility in water across the physiological pH range. The most important variable that must be controlled to assure safety and efficacy is the purity [redacted] . The synthetic and purification processes have been demonstrated to produce drug substance of high purity, [redacted]

[redacted] at scales up to the intended commercial range.

The development of the synthetic process is thoroughly documented, to provide understanding of how Critical Quality Attributes such as impurity levels are controlled. Purge studies have been performed to insure that the acceptance criteria for impurities in the isolated intermediates, combined with the capability of the purification processes, provide assurance that any impurities in the drug substance are at a safe level. Chromatographic impurity tests on the drug substance provide an additional level of assurance, and there are no related substances above the ICH qualification levels (0.15%) in the drug substance. Residual solvents, inorganics and other impurities are also controlled to safe levels in the drug substance.

Maraviroc drug substance is very stable, with stress studies show essentially no degradation except under oxidizing conditions where a pair of amine oxides are formed. The only trend observed under long-term (25°C/60%RH and 30°C/65%RH for 12 months) and accelerated stability studies (40°C/75%RH for 6 months) was a slight decrease in [redacted] and a retest date [redacted] is supported by these studies.

(2) Drug Product

The commercial products are two film-coated immediate-release tablets, with 150 mg and 300 mg strengths. The highly soluble DS and immediate-release tablet design give pharmaceutical performance similar to oral solution. Safety and efficacy are therefore chiefly controlled by dose, dosing frequency and ADME. Pfizer indicates that maraviroc has low permeability (BCS class 3) with an absolute bioavailability of approx 23%. While a clear dose-response was seen in clinical studies, maraviroc is not a narrow therapeutic range drug, and normal pharmaceutical quality controls for assay, content uniformity and dissolution are adequate to assure the efficacy and safety described in the labeling, when operating within the proposed design space.

Dosage form quality and performance is assured by a well-controlled manufacturing process combined with conventional end-product testing for verification. The main innovative aspect of quality control used for this NDA is the development of Design Spaces for the manufacturing processes of both drug substance and product. This is described in Section III C, below.

Dissolution is rapid (approx [redacted] in 15 min; basket at 100 rpm in 0.01M HCl), and was not influenced significantly by manufacturing parameters within their design space ranges, [redacted]. A conventional approach to assuring content uniformity (USP <905> [redacted]) is appropriate given the high drug load [redacted], and assurance is further strengthened by the developmental studies reported in this NDA.

Packaging configurations are [redacted] bottles of [redacted] 60 for both 150 and 300 mg strengths, with child resistant closures and induction-sealed liners [redacted]

No differences in stability were seen between different strengths or packaging configurations. While some variation in assay and dissolution were observed, no trends were found. Assay values remained fairly constant and there was no increase in degradants, so an expiry of 24 months can be granted as per ICH Q1E in all proposed packaging configurations based on 12 months of long-term data (25°C/60%RH and 30°C/65%RH) and 6 months of accelerated data.

[redacted]

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

Maraviroc Tablets, in combination with other antiretroviral agents, is indicated for treatment-experienced adult patients infected with CCR5-tropic HIV-1 who have HIV-1 strains resistant to multiple antiretroviral agents. The two strengths, 150 and 300 mg, allow for dose adjustments needed due to drug-drug interactions:

- 150 mg twice daily when dosed with a CYP3A4 inhibitor
- 300 mg twice daily without an inhibitor or inducer of CYP3A4
- 600 mg twice daily when dosed with a inducer of CYP3A4

Bottles of 60 tablets provide a 30-day supply for the 150 mg BID and 300 mg BID dosing levels, and a 15-day supply at the highest dose recommended (600 mg BID).

Both tablets are blue, film-coated oval debossed with "Pfizer" on one side and "MVC 150" or "MVC 300" on the other side.

The stability data supports an expiration dating period of 24 months when stored at 25°C (77°F); excursions permitted between 15° and 30°C (59°-86°F) [see USP Controlled Room Temperature], in bottles [redacted].

C. Basis for Approvability or Not-Approval Recommendation

The conventional elements of quality control presented in this NDA support Pfizer's ability to manufacture maraviroc tablets with consistent quality and performance. Inspections were carried out at both the drug substance and drug product manufacturing sites, and both facilities were judged to be acceptable. The majority of our communication with Pfizer related to the design space aspects, however a number of

questions and recommendations related to other issues were conveyed. Questions related to in-process tests, how the risk from several potential impurities was managed, disparities between assay and content uniformity for some tablet batches, [redacted] were sent, and adequate responses were received.

The major innovative aspect of quality control which was emphasized in this PQAS Pilot application was the development of design spaces for the manufacturing parameters. Pfizer employed knowledge of the current product and past experience to identify drug substance and drug product Critical Quality Attributes (CQAs). These are the physical and chemical properties of the drug substance and drug product that are essential to product performance with respect to safety and efficacy. A risk assessment technique was then carried out to identify the process parameters that have an influence on the CQAs. Details of the risk methodology were submitted in response to the IR letter. Design spaces for the selected parameters for both drug substance as well as drug product were developed using a combination of univariate and multivariate Design Of Experiments. It is felt that this approach provides more depth of understanding than would be apparent in a conventional NDA. However, some uncertainty remained within the design spaces due to interactions and scale factors that were not fully explored even within this thorough a development program, which includes some experience at commercial scale and site. Through the written communication with Pfizer and the direct observations and discussions during the inspections, enough understanding of the overall quality control approach for maraviroc was obtained to convince FDA that safety and efficacy will be assured as the design spaces are implemented in commercial operation.

Documentation in the NDA of the plans for non-routine testing was judged to be important when the design space was supported primarily by smaller scale studies or univariate studies, or where this information was judged to be needed based on the detectability, probability, and severity of impact on safety or efficacy.

Assurance that Pfizer's overall quality control approach will handle appropriately the residual uncertainties in the design space was obtained from a number of sources:

- The scientific approach to product and process development outlined in the Pharmaceutical Development Report (See P.2.3) and in the Manufacturing Process Development Section (See S.2.6)
- Responses to our March 29 questions on change control when moving within the design space to an area which has not been explored in commercial conditions (See discussion of Process Optimization in P.2.3.2.)
- Dialog during inspection on Pfizer's approach to change control and knowledge management for the drug product design space (See discussion in P.2.3.3 Focus Area 1)
- FDA recommendations and response about [redacted] with some potential to impact DS [redacted] (See discussion in P.2.1.1)

One goal of the PQAS NDA Pilot program is to explore review approaches that can improve communication between FDA and Applicants, and between FDA Offices. We have used two approaches that we believe strengthen both communication and quality assurance:

- Participation of review team members in both Pre-Approval Inspections (PAIs) allowed further understanding of Pfizer's overall quality control strategy to be incorporated into the application review. Information exchange prior to the PAI, including a face-to-face meeting of the full CMC team (ORA, CDER Compliance, and ONDQA), and communication after the PAI benefited all participants.
- We have included a focused summary designed to convey our conclusions to FDA's Office of Regulatory Affairs and CDER Office of Compliance so that future inspections can include what we consider to be the most important design space parameters and issues (see Appendix 2). This may also be useful for future ONDQA reviews

Because implementation of regulatory agreements for individual products is not yet possible, we are approving the design space ranges based on existing regulation. Once action is taken on NDA 22-128, we will consider the Proven Acceptable Ranges (PAR) / Design Space Ranges in Tables 2.3.S.2-4, 2.3.S.2-13, 2.3.S.2-15 and 2.3.S.2-22 (for drug substance) and in Table 2.3.P.2.3-24 (for drug product) to be "variations already provided for in the application" [see 21CFR314.70(a)], movement within which will be managed by Pfizer's quality control system. Further refinement of post-approval communication related to management of the design space will be pursued once product-specific regulatory agreements are implemented (See discussion in P.3.3).

In summary, Pfizer's overall quality control strategy for maraviroc is judged to provide a high level of assurance that this product will consistently meet the safety and efficacy standards established by its clinical studies. Important elements of this control strategy include:

- Determination of CQA based primarily on safety and efficacy
- Risk assessment to develop and refine the design spaces for the manufacturing processes
- Control of impurities close to the point of origin
- Specifications for starting materials, intermediates, drug substance and drug product based on the process design and capability
- In-Process Controls on reaction completion (identified during PAI — [redacted])
- In-Process Controls during tablet manufacturing (managed through the batch record)
- A knowledge management approach to insure that information obtained during development is available as the commercial process is verified and optimized

It is the overall control strategy that provides strong assurance of consistent performance of maraviroc tablets.

III. Administrative

A. Reviewer's Signature: electronically signed in DFS

Donna Christner, Ph.D.

Sharmista Chatterjee, Ph.D.

Stephen Miller, Ph.D.

B. Endorsement Block: electronically signed in DFS

Elaine Morefield, Ph.D.

C. CC Block: entered electronically in DFS

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Withheld Track Number: Chemistry- 1

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/s/

Stephen Paul Miller
6/15/2007 03:55:27 PM
CHEMIST
Review Complete; CMC Recommendation is Approval

Donna Christner
6/15/2007 03:57:51 PM
CHEMIST

Sharmista Chatterjee
6/15/2007 04:05:38 PM
CHEMIST

Elaine Morefield
6/18/2007 08:50:38 AM
CHEMIST
Just received notification that the approved tradename will be Selzentry.