CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-743

Chemistry Review(s)

NDA 21-743

Addendum to CMC Review

Drug Name: Tarceva
Review Date: October 12, 2004
Reviewer: Nallaperumal Chidambaram Ph.D.

Background: This is an addendum to review #1 written by Li-Shan Hsieh, Ph.D., to include the following:

(1) Overall recommendation from the office of compliance.
(2) Incorporate changes to established name as recommended by Dr. John Simmons, Director, Division of New Drug Chemistry I and to be in conformity with current thinking within the Office of New Drug Chemistry.

Review Notes:

The office of compliance had not provided an overall acceptable recommendation when review #1 was signed off into DFS. The clinical division would like to take an action on this application anytime soon. The primary reviewer was aware of clinical divisions' intention when she went on a vacation. She is currently out of the country and wanted me to write an addendum as soon as we receive an acceptable recommendation from the office of compliance. The report is attached at the end of this addendum.

Labeling: The applicant proposed [ ] as the established name for Tarceva; Dr. John Simmons, Director, Division of New Drug Chemistry I indicated that ONDC and OGD Chemistry Division Director's have decided henceforth to list established name as a free base or a free acid. Based on his directive, we recommend that the established name be changed from [ ] to erlotinib. The applicant in a letter dated October 11, 2004 has indicated acceptance of our recommendation to change the established name to erlotinib.

Conclusions and Recommendations: The office of compliance has provided an overall acceptable recommendation and the applicant has indicated to change the established name from [ ] to erlotinib. If the applicant has printed labels to include established name as [ ], it is acceptable to market with those labels and change the established name to erlotinib at next printing. This application is recommended for approval from the standpoint of chemistry, manufacturing and controls.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21743/000
Org Code : 150
Priority : 1P

Sponsor: OSI PHARMS
58 SOUTH SERVICE RD STE 110
MELVILLE, NY 11747

Stamp Date : 30-JUL-2004
PDUFA Date : 30-JAN-2005
Action Goal :
District Goal: 02-MAR-2004

Brand Name ; TARCEVA (ERLOTINIB 25/100/150MG TAB
Estab. Name:
Generic Name: ERLOTINIB HCL
Dosage Form: (TABLET)
Strength : 25, 100, AND 150 MG

FDA Contacts: P. ZIMMERMAN Project Manager (HFD-150) 301-594-2479
L. HSIEH Review Chemist (HFD-150) 301-594-0497
M. CHIDAMBARAM Team Leader (HFD-810) 301-594-5351

Overall Recommendation: ACCEPTABLE on 30-SEP-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-MAY-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-MAY-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN FEI :

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-SEP-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTX OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-MAY-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1819171 FEI : 1819171
SCHWARZ PHARMA MANUFACTURING INC
120 E 3RD ST/1101 C AVE
SEYMOUR, IN 472[redacted]
DMF No: [redacted] AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCH OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-SEP-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI

DMF No: AADA:

Responsibilities: —

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-MAY-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DMF NO: AADA:

Responsibilities:

Profile	:	CSN	OAI Status: NONE
Last Milestone:		OC RECOMMENDATION	
Milestone Date:		10-MAY-04	
Decision	:	ACCEPTABLE	
Reason	:	DISTRICT RECOMMENDATION	

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

/s/

Nallaperumal Chidambaram
10/12/04 04:26:46 PM
CHEMIST

Hasmukh Patel
10/12/04 04:29:37 PM
CHEMIST

Withheld

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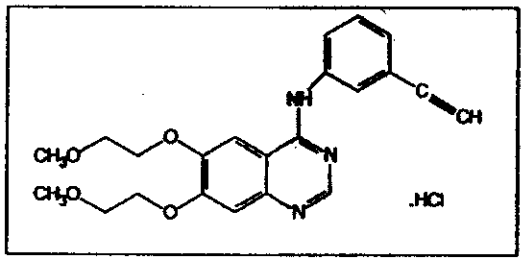
page(s) of trade secret and/or confidential commercial information

DMF

(b4)

NDA 21-743

Tarceva™



OSI Pharmaceuticals Inc.

Li-Shan Hsieh, Ph. D.
Division of Oncology Drug Products HFD-150

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Chemistry Review Data Sheet

1. NDA 21-743

2. REVIEW: 1

3. REVIEW DATE: 22-Sep-2004

4. REVIEWER: Li-Shan Hsieh, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC pre-meeting	Meeting date: 9-Jul-2002
IND 53,728 (SN 205), [ ]	Letter date: 26-Aug-2002, Review date: 24-Oct-2002
CMC pre-NDA meeting	Meeting date: 11-Jul-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
001 (RRZ)	20-Jan-2004
005 (RRC) Added [ ] facility	24-May-2004
006 (RRC) Tablet imprint change	03-Jun-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	OSI Pharmaceuticals Inc.
Address:	58 South Service Road (Suite 110), Melville, New York, USA 11747
Representative:	Christine Boisclair, Senior Director, Global Regulatory Affair
Telephone:	631-962-2156, Fax: 631-962-2076

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Tarceva™
b) Non-Proprietary Name (USAN):	Erlotinib hydrochloride
c) Code Name/# (ONDC only):	OSI-774-01

[redacted]

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION:

Tarceva received fast-track designation from the Agency on 5-Sep-2002 for the indication "2nd/3rd line NSCLC under Paragraph 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act 21 CFR 314.50 and 21 CFR 314 Subpart H Accelerated approval of New Drug. The rolling NDA application was agreed to in a pre-NDA meeting on December 10, 2003. The CMA Pilot 1study was agreed on 24-Jun-2004. Exclusive marketing rights: Section 527 of the FFDCA (21 U.S.C. 360 cc)
User Fee waiver: section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act.

10. PHARMACOL. CATEGORY: Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor

11. DOSAGE FORM: Film-Coated Tablets

12. STRENGTH/POTENCY: 25 mg, 100 mg, and 150 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _xx_ Rx ___OTC

15. SPOTS ([redacted]):

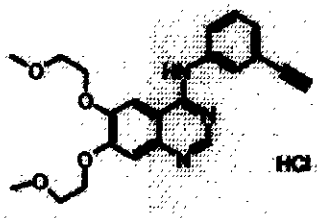
_____SPOTS product – Form Completed
__xx__Not a SPOTS product

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

Chemical name:

N-(3-Ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride

Chemical Structure:



Molecular formula: $C_{22}H_{23}N_3O_4.HCl$

[redacted]

Molecular weight: Salt 429.90
Free base 393.43

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			1	Adequate	13-Jul-2004	Review by Dr. L. Hsieh
	III			3	Adequate	26-Sep-2000	Review by Dr. D. Klein
	III			1	Adequate	19-Jul-2004	Review by Dr. L. Hsieh
	III			1	Adequate	26-Jul-2004	Review by Dr. L. Hsieh

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

REVIEWS			
Microbiology (sterility assurance)	N/A		
EES	Pending		
ODS	Pending		Jennie Chang/ Charlie Hoppes
LNC	Acceptable	06-Sep-2004	Dr. Guirag Poochian
Pharm/Tox	Pending		Dr. Kimberly Benson
Biopharm	Pending		Dr. Gene Williams
Methods Validation	N/A		
EA	Adequate	22-Sep-2004	Dr. Li-Shan Hsieh
Biostatistics (CMC statistics)	N/A		

19. ORDER OF REVIEW (OGD Only)

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 21-743

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC information provided has been reviewed and found adequate. The approval is contingent upon (1) an overall acceptable recommendation from the Office of Compliance and (2) an acceptance of dissolution specification change recommended by Biopharm. Most facilities have been found acceptable and only one facility is still pending. Therefore, this NDA is recommended for **Approvable** from CMC standpoint.

B. Post Marketing (Phase 4) CMC-related Commitments, Agreements, and/or Risk Management Steps, if recommendation is for Approval

II. Summary of Chemistry Assessments

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

The active ingredient of TARCEVA is erlotinib hydrochloride. Erlotinib hydrochloride is an USAN name. The active moiety of this monhydochloride salt, erlotinib, is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4.HCl$ and a molecular weight of 429.90. Erlotinib hydrochloride has a pK_a of 5.42 at 25°C. Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane. Aqueous solubility of erlotinib hydrochloride is pH dependent with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2.

TARCEVA tablets are available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg or 164 mg) equivalent to 25 mg, 100 mg or 150 mg of erlotinib and inactive ingredients. Standard pharmaceutical excipients are used including: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. 100mg and 50 mg tablets have a common composition where the drug substance: [ ] In order to ensure a suitable size for the 25 mg tablet [ ] are used as tablet [ ] such that the drug substance: [ ] All tablets are round, biconvex face, straight sides, white, film-coated and are distinguished by size and color of the imprint, (— orange for 25 mg; — gray for 100 mg; and — maroon for 150 mg), of the printed tablet strength identifiers. The FD&C Yellow #6 is

used for marking purposes only. This color additive is an ingredient of the orange ink that is used to imprint, on one side of the 25 mg tablet, a "T" and "25". The same formulations have been used throughout clinical development except 25 mg tablet. The 25 mg tablet was not film-coated in the phase 1/II study but film-coated in phase III study. No comparability study is needed. All tablets are formulated for immediate release.

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

TARCEVA is intended for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. The recommended daily dose of TARCEVA is 150 mg taken at least one hour before or two hours after the ingestion of food. When dose reduction is necessary, reduce in 50 mg decrements.

C. Basis for Recommended Action

NDA 21-743 is recommended for **Approvable** from CMC standpoint based on the following:

- All CMC information is adequately provided and well studied.
- Most facilities for manufacturing and controls of drug substance and drug product are found acceptable by the Office of Compliance except one alternate facility for drug substance manufacturing which is still under inspection.
- The acceptance of dissolution specification change recommended by Biopharm

III. Administrative

A. Reviewer's Signature

Signatures are captured electronically in DFS

B. Endorsement Block

Li-Shan Hsieh/Date: Same date as draft review
Nallaperumal Chidambaram /Date
Paul Zimmerman/Date

C. CC Block

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ENVIRONMENTAL ASSESSMENT

OSI Pharmaceuticals Inc. requests a claim for categorical exclusion from the requirement to submit an Environmental Assessment, since the estimated concentration of erlotinib at the point of entry into the aquatic environment will be below 1 part per billion (21 CFR 25.31(b)).

To OSI's knowledge no extraordinary circumstances exist that would significantly affect the quality of the human environment (21 CFR 25.15 (d)).

See Chemistry Review page 69