CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-399

Chemistry Review(s)

NDA 21-399

IRESSA™ 250 mg/Brown Tablets

AstraZeneca Pharmaceuticals, LP

Chengyi Liang, Ph.D.
HFD-150 Division of Oncological Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA #:** 21-399

2. **CHEM. REVIEW#:** 2

3. **REVIEW DATE:** Oct. 15, 2002

4. **REVIEWER:** Chengyi Liang

5. **PREVIOUS DOCUMENTS**

Previous Documents	Document Date
IND [redacted]	Nov. 17, 1997

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Documnnent Date
Original	08-07-2002
Amendment RRC	04-04-2002
Amendment RRC	07-03-2002
Amendment NC	04-30-2002
Amendment	08-02-2002
Amendment	11-13-2001
Amendment RRZ	05-07-2002
Amendment BC	09-26-2002
Amendment BC	08-20-2002
Fax	10-15-2002

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

Name: AstraZeneca UK Limited

Address: Silk Rd. Business Park
Macclesfield, Cheshire SK10 2NA
England

Representative: AstraZeneca Pharmaceuticals LP
Mark Scott Ph.D.
Executive Director, Regulatory Affairs
1800 Concord Pike P.O.Box 8355
Wilmington, DE 19803-8355

Telephone: 302-886-8495

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary: IRESSA
b. Nonproprietary Name/USAN: Gefitinib
c. Code Name/#: ZD1839
d. Chem. Type/Submission Priority

Chem. Type 3
Submission Priority P

9. LEGAL BASIS FOR SUBMISSION: Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY/INDICATION: Cytostatic EGTR inhibitor for the treatment in cancer patients with a broad range of solid tumor types

11. DOSAGE FORM: Tablet

12. STRENGTHS/POTENCY: 250 mg/brown tablets

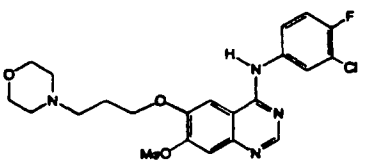
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) No

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

4-(3-Chloro-4-flurophenylamino)-7-methoxy-6-(3-(4-morpholinyl)propoxy)quinazoline



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			1	adequate	R. Frankewich, HFD-180 8/17/00	None
	III			1	adequate	G. Chen HFD-180 9/2/97	None
	III			1	adequate	S.Zuk, HFD-643 5/1/2000	None
	III			1	adequate	D.Klein 2/9/2001	None
	III			1	adequate	J. Boal HFD-580 8/8/01	None

B. INDs:

Document	Application Number	Description
IND	[redacted]	IRESSA has been used in a lot of physician INDs

18. CONSULTS:

Consult	Status	Comments
EER	Acceptable	
Trade Mark	Pending	IRESSA was found to be unacceptable by Nomenclature Committee. It will be overwritten by Oncology Division director.
Methods Validation	Pending	Validation package will be submitted after the approval of this NDA.
EA	Categorical Exclusion	Acceptable
Microbiology	Acceptable	

The Chemistry Review for NDA 21-399

The Executive Summary

I. Recommendations

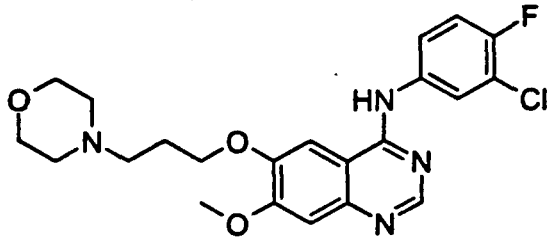
A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval based on the submitted CMC information. All the remaining deficiencies related to the drug substance and drug product have been satisfactorily addressed.

II. Summary of Chemistry Assessments

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

Gefitinib is an anilinoquinazoline with the chemical name N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoline-4-amine and the following structural formula:



It has the molecular formula $C_{22}H_{24}ClFN_4O_3$ and is a white-colored powder. Gefitinib is a free base. The molecule has pK_as of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Gefitinib can be defined as sparingly soluble at pH 1, and is practically insoluble above pH 7, with the solubility dropping sharply at pH 5. In non-aqueous solvents, gefitinib is freely soluble in glacial acetic acid and dimethylsulphoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.

The final drug substance is manufactured in the UK.

The proposed drug substance specifications are found to be adequate and test data are acceptable. The drug substance is retested at 24 months and is stored at controlled room temperature.

The drug product for the clinical trials is brown film-coated tablets.

The bulk brown DP tablets will be packed into 75 ml — bottle in a Delaware facility. Up to — months stability data from the supportive DP batches (brown DP batches are adequate to demonstrate the stability of DP tablets under various testing conditions. No significant degradation in chemical and physical properties has been observed during the stability studies. However, the limited 3 months primary stability data from 3 commercial brown DP tablets batches are available currently. Eighteen months shelf life for the brown DP tablets is granted based on the available stability data.

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

Gefitinib is an inhibitor tyrosine kinase, which is commonly over expressed, in solid human tumors of epithelial origin. In preclinical studies, inhibition of tyrosine kinase activity inhibits tumor growth, metastasis and angiogenesis and increases tumor cell apoptosis. It enhances the anti-tumor activity of chemotherapy, radiotherapy and hormonal therapy.

The recommended daily dose of IRESSA is one 250 mg tablet with or without food.

C. Basis for Approvability Recommendation

The applicant has addressed satisfactorily the deficiencies found in CMC review. The agreements to provide the required information are also acceptable. Based on the information and commitments, this NDA is recommended to be approved.

III. Administrative

A. Reviewer's Signature

S

Chengyi Liang, Ph.D., Review Chemist

Richard Lostritto, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 21-399
HFD-150 Division File
HFD-150/CLiang
HFD-150/RLostritto
HFD-150/ABaird

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/s/

Chengyi Liang
4/29/03 12:43:21 PM
CHEMIST

Richard Lostritto
5/1/03 01:46:47 PM
CHEMIST

NDA 21-399

IRESSA™ 250 mg/Brown Tablets

AstraZeneca Pharmaceuticals, LP

Chengyi Liang, Ph.D.
HFD-150 Division of Oncological Drug Products

Table of Contents

Chemistry Review Data Sheet

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4. **REVIEWER:** Chengyi Liang

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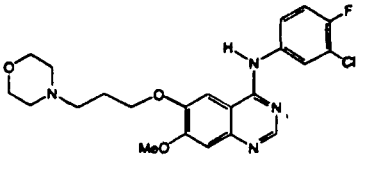

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[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. INDs:

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APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-399

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended to be approvable based on the submitted CMC information and the minor remaining deficiencies. All deficiencies related to the drug substance and drug product have been addressed during the submission through timely and proactive communication. The applicant committed to address the remaining approvable related issues and to provide updated stability test data for the drug product tablets.

II. Summary of Chemistry Assessments

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

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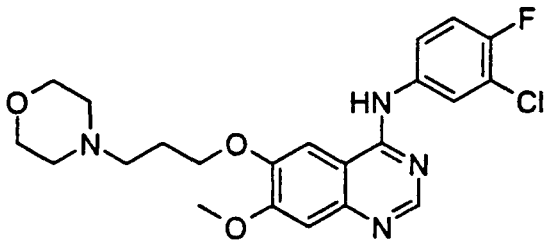

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The recommended daily dose of IRESSA is one 250 mg tablet with or without food.

C. Basis for Approvability Recommendation

Outstanding minor deficiencies persist, therefore, the recommendation is Approvable.

III. Administrative

A. Reviewer's Signature

/S/

Chengyi Liang, Ph.D., Review Chemist

/S/

Richard Lostritto, Ph.D.
Chemistry Team Leader

B. Endorsement Block
Chemist Name/Date: Chengyi Liang, Ph.D.
Chemistry Team Leader Name/Date: Richard Lostritto, Ph.D.
Project ManagerName/Date: Amy Baird

C. CC Block
CC:
Orig. NDA 21-399
HFD-150 Division File

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/s/

Chengyi Liang
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CHEMIST

Richard Lostritto
10/18/02 10:21:32 AM
CHEMIST