

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206995Orig1s000

CHEMISTRY REVIEW(S)

NDA 206995-Orig1-New/NDA(1)

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - (b) (4)

Facility DUNS Number: (b) (4)	Action Indicated Status: None	
District Office Recommendation: Approve Facility	District Office Recommendation Reasons: Based on File Review	District Office Decision Factors:
Office of Process and Facilities Recommendation: Approve Facility	Office of Process and Facilities Recommendation Reasons: District Recommendation	Office of Process and Facilities Re-Evaluation Date: (b) (4)

ASTRAZENECA PHARMACEUTICALS LP | 2517100 | TCM TABLETS, PROMPT RELEASE | Approve Facility - 2015-11-10

ASTRAZENECA UK LTD | 3002850317 | TCM TABLETS, PROMPT RELEASE | Approve Facility - 2016-04-11

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - (b) (4)

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - (b) (4)

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Overall Application Re-evaluation Date
7/18/15

Cancel

NDA 206995-Orig1-New/NDA(1)

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - 2015-07-18 ▾

ASTRAZENECA PHARMACEUTICALS LP | 2517100 | TCM TABLETS, PROMPT RELEASE | Approve Facility - 2015-11-10 ▾

Facility DUNS Number: 054743190	Action Indicated Status: None	
District Office Recommendation: Office of Process and Facilities Approve Facility	District Office Recommendation Reasons: Office of Process and Facilities Recommendation Reasons: Based on Profile	District Office Decision Factors: Office of Process and Facilities Re-Evaluation Date: 2015-11-10

ASTRAZENECA UK LTD | 3002850317 | TCM TABLETS, PROMPT RELEASE | Approve Facility - 2016-04-11 ▾

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - (b) (4)

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ASTRAZENECA PHARMACEUTICALS LP 2517100 TCM TABLETS, PROMPT RELEASE	Approve Facility - 2015-11-10
ASTRAZENECA UK LTD 3002850317 TCM TABLETS, PROMPT RELEASE	Approve Facility - 2016-04-11

Facility DUNS Number: 232784079	Action Indicated Status: None	
District Office Recommendation: Approve Facility	District Office Recommendation Reasons: Based on File Review	District Office Decision Factors:
Office of Process and Facilities Recommendation: Approve Facility	Office of Process and Facilities Recommendation Reasons: District Recommendation	Office of Process and Facilities Re-Evaluation Date: 2016-04-11

(b) (4)	CSN NON-STERILE API BY CHEMICAL SYNTHESIS Approve Facility - (b) (4)
(b) (4)	CSN NON-STERILE API BY CHEMICAL SYNTHESIS Approve Facility - (b) (4)

Overall Manufacturing Inspection Recommendation

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Facility DUNS Number:

Action Indicated Status: None

(b) (4)

District Office Recommendation:
Approve Facility

District Office Recommendation Reasons:
Based on File Review

District Office Decision Factors:

Office of Process and Facilities Recommendation:
Approve Facility

Office of Process and Facilities Recommendation Reasons:
Based on File Review

Office of Process and Facilities Re-Evaluation Date:
(b) (4)

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility - (b) (4)

Overall Manufacturing Inspection Recommendation

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Overall Application Re-evaluation Date

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Facility DUNS Number: (b) (4)	Action Indicated Status: None	
District Office Recommendation: Approve Facility	District Office Recommendation Reasons: Based on File Review	District Office Decision Factors:
Office of Process and Facilities Recommendation: Approve Facility	Office of Process and Facilities Recommendation Reasons: District Recommendation	Office of Process and Facilities Re-Evaluation Date: (b) (4)

Overall Manufacturing Inspection Recommendation

Approve
 Withhold

Overall Application Re-evaluation Date
 7/18/15 

Cancel

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

/s/

MARY GRACE LUBAO
07/21/2015

NDA 206-995

IRESSA (Gefitinib)

Tablet

250 mg

AstraZeneca UK Limited

Division of Oncology Drug Products

Donghao (Robert) Lu, Ph.D.
Division of New Drug Products 1
Office of New Drug Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	7
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S. DRUG SUBSTANCE.....	10
P. DRUG PRODUCT	17
A. APPENDICES	20
R. REGIONAL INFORMATION	20
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	20
A. Labeling & Package Insert	20
B. Environmental Assessment Or Claim Of Categorical Exclusion	23
III. List Of Deficiencies And Responses	23



Chemistry Review Data Sheet

1. NDA 206-995
2. REVIEW NUMBER: 1
3. REVIEW DATE: 12 May 2015
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS**DOCUMENT DATE**

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED**DOCUMENT DATE**

NDA 206-995, 000

17-Sep-2014

IND 120,992, 007

07-May-2014

7. NAME & ADDRESS OF APPLICANT:

NAME:

AstraZeneca UK Limited

ADDRESS:Charter Way, Silk Road Business Park,
Macclesfield, Cheshire, England**REPRESENTATIVE:**Mark A. DeSiato Vice President, Global Regulatory
Affairs**TELEPHONE:**

(302) 885-1386

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME IRESSA (Gefitinib) Tablet, 250 mg
NON-PROPRIETARY NAME (USAN) Gefitinib
CODE NAME/ NUMBER (ONDC ONLY)
CHEMISTRY TYPE / SUBMISSION PRIORITY 6S

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

10. PHARMACOL. CATEGORY: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 250 mg

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed Not a SPOTS product

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

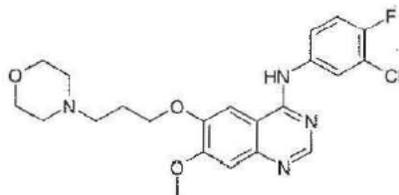
Name (USAN, INN): Gefitinib

Name (IUPAC): N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine

Name (CAS): 4-Quinazolinamine N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]

(CAS) Registry Num: 184475-35-2

Structural Formula:



Mol. Formula: C₂₂H₂₄ClFN₄O₃

Mol. Wt.: 446.90

Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	
	III			4	N/A	

Note: These DMFs are associated with the container closure system. The container closure system is used for solid oral drug products – see CMC Review MaPP.

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

Chemistry Assessment Section

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Compliance	Acceptable		R. Wittorf
Methods Validation	Acceptable		Per NDA 21-399
ODS DMEPA	Acceptable		Per NDA 21-399
EA	Acceptable		Per NDA 21-399
Biopharm	Acceptable		Per NDA 21-399
Pharm/Tox	Acceptable		Per NDA 21-399
Micro Consultation	Acceptable		Per NDA 21-399

Overall Manufacturing Inspection Recommendation

Task Summary | Task Details | Updates | Issues | **Inspection Management Form**

Inspection Management Form (As of 9:16 AM)

Inspection Management Form

NDA 206995-Orig1-Rew/NDA(1)

(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility

(b) (4)

ASTRAZEECA PHARMACEUTICALS LP | 2517100 | TCM TABLETS, PROMPT RELEASE | Approve Facility - 2015-11-10

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(b) (4) CSN NON-STERILE API BY CHEMICAL SYNTHESIS | Approve Facility (b) (4)

Overall Manufacturing Inspection Recommendation

Approve
Withhold

Overall Application Re-evaluation Date: 7/15/16

Assigned To: **Robert Wittorf**

✓ Edit Assignment

This was done on **May 12, 2015** (Today)

Status: **Complete**

This task is waiting on 2 tasks

Last Update: May 12, 2015 | Submitted On: Sep 25, 2014

Reference Number: 1959803

The Chemistry Review for NDA 206-995

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Chemistry Assessment Section

The drug product IRESSA (Gefitinib) Tablet, 250 mg, is recommended as APPROVAL from a CMC perspective.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is Gefitinib. It is a free base. The chemical name is N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine. It has a molecular formula of $C_{22}H_{24}ClFN_4O_3$ and its molecular weight is 446.90. The drug substance specification includes: description, identification, assay, impurities, residual solvents, residue on ignition, water content, and particle size distribution. The drug substance is physically and chemically stable based on evaluation of the testing data.

2. Drug Product

The drug product is IRESSA[®] (gefitinib) tablets contain 250 mg of gefitinib and is available as brown film-coated tablets. It is intended for oral administration.

IRESSA 250 mg tablets are packed in square, white, 75 ml, high-density polyethylene (HDPE) bottles with (b) (4) cap. (b) (4)

(b) (4) Each bottle contains 30 tablets. The drug substance has a retest period of (b) (4)

The inactive ingredients of IRESSA tablets consist of: (1) Tablet core: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate; (2) Coating: hypromellose, polyethylene glycol 300, titanium dioxide, red ferric oxide and yellow ferric oxide. The drug product is physically and chemically stable based on evaluation of the testing data. The drug product has a shelf life of 48 months.

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

Iressa is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations. The recommended dose of Iressa is 250 mg orally, once daily with or without food. Dosing can be withheld for up to 14 days if poorly

Chemistry Assessment Section

tolerated diarrhea or skin reactions develop. Iressa is supplied as bottles of 30 tablets. The drug product should be stored at controlled room temperature 20-25°C (68-77°F) [see USP].

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, AstraZeneca has submitted sufficient and appropriate information to support the approval of the drug product. Iressa (gefitinib) 250 mg tablets was approved for marketing with NDA 21-399 on May 5, 2003, for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The NDA 21-399 was voluntarily withdrawn on April 25, 2012. AstraZeneca submitted an IND amendment to Iressa pre-IND 120,992 on May 7, 2014 (Sequence 0007), describing the differences in CMC and facilities between NDA 21-399 and this NDA 206-995. Based on the evaluation, the drug product Iressa tablets, 250 mg, is recommended as APPROVAL from a CMC perspective.

During the review, risk based approaches have been used to assess the product development, manufacturing process and quality control. As this is a previously approved drug product, the review focuses on the difference between the two NDAs (including the NDA 21-399 supplements).

III. Administrative**A. Reviewer's Signature**

\s\ Donghao (Robert) Lu, Ph.D.

Donghao R.
Lu -S

Digitally signed by Donghao R. Lu -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Donghao R. Lu
-S,
0.9.2342.19200300.100.1.1=1300377481
Date: 2015.05.13 13:15:19 -04'00'

B. Endorsement Block

\s\ Olen Stephens, Ph.D.

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People, cn=Olen
Stephens -S,
0.9.2342.19200300.100.1.1=200055882
Date: 2015.05.13 13:16:19 -04'00'

C. CC Block

Chemistry Assessment

Review Note:

This is a previously approved drug product. IRESSA (gefitinib) 250 mg tablets (NDA 21-399) received accelerated approval on May 5, 2003 under 21 CFR 314, subpart H, as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The NDA 21-399 was voluntarily withdrawn on April 25, 2012 (date of the Federal Register Notice) by AstraZeneca Pharmaceuticals. (b) (4)

AstraZeneca submitted this application (NDA 206-995) for IRESSA (gefitinib) 250 mg tablets for the following indication: IRESSA (gefitinib) is indicated for the first-line treatment of patients with (b) (4) metastatic non-small-cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test.

Upon recommendation by FDA (refer to pre-NDA Type B meeting minutes of March 11, 2014 between FDA and AstraZeneca), AstraZeneca submitted an IND amendment to IRESSA pre-IND 120,992 on May 7, 2014 (Sequence 0007), describing the differences in CMC and facilities between NDA 21-399 and the proposed NDA 206-995, with the objective of aiding review of NDA 206-995. This amendment was reviewed by the Agency and no issues were identified.

The key changes are:

- Replacement of AstraZeneca Macclesfield, UK as site of gefitinib drug substance manufacture (b) (4). (b) (4). Although the site of manufacture has changed, the manufacturing process and controls remain unchanged.
- Updated impurity assessment.
- Changes to the container/closure system (b) (4) for drug substance.
- Inclusion of an additional supplier of the starting material (b) (4). The specification remains unchanged.
- Data for new and more recent drug substance batches.
- Removal of (b) (4) at AstraZeneca Macclesfield, UK for drug product manufacture of commercial supplies.
- Data for new and more recent drug product batches.

In addition, the Quality Control and Analytical Testing sections have been updated in line with current pharmacopeial expectations.

The discussion of impurities for drug substance and drug product has been extended to take account of new and evolving regulatory guidance since the approval of NDA 21-399 in 2003, specifically:

- ICH Q3D (Step 2) Draft Consensus Guideline for Elemental Impurities.

Chemistry Assessment Section

- o ICH M7 (Step 2) Consensus Guideline: Assessment and Control of NDA reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

A comprehensive, risk-based approach to identify potential mutagenic impurities (PMI) and mutagenic impurities (MI) in the drug substance and drug product is further described. The outcome of this assessment is summarized in '2.3.S.3.2 Impurities'. (b) (4)

This review will focus on these changes. However, additional review was performed regarding the use of the tablets dispersed in water for oral administration.

I. Review of CTD - Module 3: Quality: Body Of Data

S. DRUG SUBSTANCE

S.1 General Information

S.1.1 Nomenclature

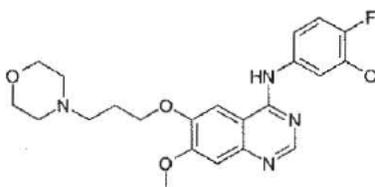
USAN, INN: Gefitinib

Chemical name (IUPAC): N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine

Chemical Abstracts name (CAS): 4-Quinazolinamine N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]

CAS registry number: 184475-35-2

S.1.2 Structure



Gefitinib has a Mol. formula of C₂₂H₂₄ClFN₄O₃ and a relative Mol. mass of 446.90.

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Chemistry Assessment Section

P. DRUG PRODUCT

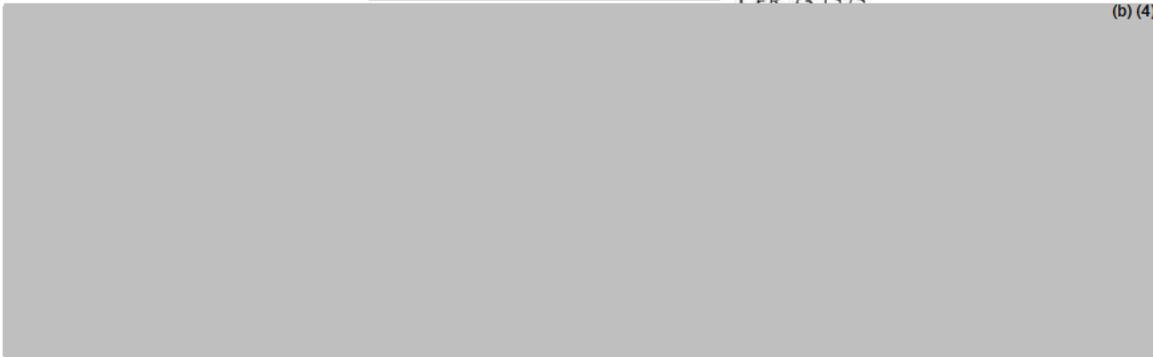
P.1 Description and Composition of the Drug Product

The drug product is provided as round, biconvex, brown film-coated tablets containing 250 mg of gefitinib. It is intended to be used for oral administration. The tablets have a diameter of approximately 11 mm and are (b) (4). The name 'IRESSA' and a tablet strength marking '250' are impressed on one side; the other side is plain. The components and compositions of gefitinib tablets are listed below.

Table 1 **Composition of IRESSA 250 mg film-coated tablets**

Ingredient	Quantity (mg/tablet)	Function	Reference to standards	
Tablet core				
Gefitinib	250.0	Drug substance	AstraZeneca standard	
Lactose monohydrate		(b) (4)	USNF	
Microcrystalline cellulose		USNF		
Croscarmellose sodium		USNF		
Povidone		USP		
Sodium lauryl sulphate		USNF		
Magnesium stearate		USNF		
Nominal core tablet weight				
Tablet coating				
Hypromellose ^a				USP
Polyethylene glycol 300				USNF
Red ferric oxide ^a			USNF, 21 CFR 73.1200	
Yellow ferric oxide ^a			USNF, 21 CFR 73.1200	
Titanium dioxide ^b			USP, 21 CFR 73.575, 21 CFR 73.1575	

(b) (4)



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Chemistry Assessment Section

Table 1 Control tests and specification for IRESSA 250 mg tablets

Test method	Specification
Description	Round, biconvex, brown, film-coated tablet intagliated with 'IRESSA' and '250' on one side and plain on the other
(b) (4)	

P.5.5 Discussion on elemental impurities

(b) (4)

Evaluation: Acceptable.

P.8.1 Integration of results for additional data points

The overall stability studies have completed and (b) (4) 48 month data respectively are provided. The shelf life remains unchanged at 48 months. *Evaluation:* Acceptable.

A. APPENDICES n/a (Per NDA 21-399)

R. REGIONAL INFORMATION n/a (Per NDA 21-399)

II. Review Of CTD -- Module 1: Prescribing Information**A. Labeling****A.1 Trade name**

There is no concern on the trade name.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Chemistry Assessment Section

Evaluation: The studies adequately supported the use of the tablets (b) (4) in water from the physiochemical point of view. It should be noted that the clinical pharm review has captured the study in which bioequivalence between the tablet and either drink liquid or liquid through a nasogastric tube has been demonstrated. (b) (4)
(b) (4). Refer to labeling review by DMEPA

A.3 Label

The draft carton and container labels for IRESSA tablets were submitted and can be seen below.

Evaluation: Acceptable.

**B. Environmental Assessment Or Claim Of Categorical Exclusion**

The categorical exclusion was requested. A statement was provided that "AstraZeneca requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (b). To the best of the sponsor's knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21(a), exist relative to this action." **Evaluation:** Acceptable.

III. List Of Comments

None (All changes, as described in Summary of changes between NDA 21-399 and NDA 206-995, are acceptable).