CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-399

Administrative Documents

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
A 21-399	Efficacy Supplement Type SE-	Supplement Number	
Drug: **IRESSA (gefitinib) Tablets**		Applicant: **AstraZeneca Pharmaceuticals**	
RPM: **Amy Baird**		HFD-**150**	Phone # **594-5779**
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (✓) Priority
• Chem class (NDAs only)	**1**
• Other (e.g., orphan, OTC)	**N/A**
❖ User Fee Goal Dates	**5-5-03**
❖ Special programs (indicate all that apply)	( ) None Subpart H (✓) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) (✓) Fast Track (✓) Rolling Review
❖ User Fee Information	
• User Fee	(✓) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (✓) No
• This application is on the AIP	( ) Yes (✓) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(✓) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
Exclusivity Summary (approvals only)	✓
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

General Information	
Actions	
• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter (✓) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (✓) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	✓
• Most recent applicant-proposed labeling	✓ 4-3-03
• Original applicant-proposed labeling	✓
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS (4-14-03; 10-9-02; 8-5-02) DDMAC (10-8-02)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	✓
• Applicant proposed	✓
• Reviews	See individual disciplinary reviews.
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	✓
• Documentation of discussions and/or agreements relating to post-marketing commitments	✓ 5-1-03
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	✓ 1-10-00
• Pre-NDA meeting (indicate date)	✓ 6-14-01
• Pre-Approval Safety Conference (indicate date; approvals only)	Determined that if there are no real safety concerns (including ILD) no safety conference needed.
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	9-23-02
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dep. Dir- 3-28-03
❖ Clinical review(s) *(indicate date for each review)*	MO Review - 4-1-03 Pulmonary Consult - 2-6-03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Copy from MO review (4-1-03) is provided under tab
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
❖ Statistical review(s) *(indicate date for each review)*	10-15-02 Adden #1 3-28-03 Adden #2 4-22-03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	10-16-02; 10-17-02; 2-12-03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	8-13-02; 1-29-03
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	10-18-02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Copy from CMC review (10-18-02) is provided under tab
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	9-26-02
❖ Facilities inspection (provide EER report)	Date completed: (✓) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (✓) Requested (in AP ltr) ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10-15-02
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	✓ 3-20-02

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

IRESSA™ (gefitinib) Tablets

NDA 21-399

Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

1. Trade Name:

   IRESSA™

2. Active Ingredient(s):

   gefitinib

3. Strength(s):

   250 mg tablet

4. Dosage Form, Route of Administration:

   Tablet, Oral

5. Applicant Firm Name/Holder of New Drug Application:

   AstraZeneca UK Limited
   Macclesfield, Cheshire, England

   US Agent:

   AstraZeneca Pharmaceuticals LP
   1800 Concord Pike
   Wilmington, DE 19850-5437

6. Approval Date:

   N/A

7. Applicable Patent(s):

(i) US Patent No. 5,457,105

(a) Expiration Date:

January 19, 2013 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. 5,457,105 contains drug substance claims, pharmaceutical composition claims, and method of use claims.

(c) Name of Patent Owner(s):

Zeneca Limited
Macclesfield, Cheshire, England

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

General Counsel
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

(e) Declaration:

The undersigned declares that US Patent No. 5,457,105 covers the formulation, composition, and/or method of use of IRESSA™ (gefitinib) Tablets. This product is the subject of this new drug application for which approval is being sought.

(ii) US Patent No. 5,616,582

(a) Expiration Date:

January 19, 2013 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. 5,616,582 contains method of use claims.

(c) Name of Patent Owner(s):

Zeneca Limited
Macclesfield, Cheshire, England

(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

General Counsel
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

(e) Declaration:

The undersigned declares that US Patent No. 5,616,582 covers the formulation, composition, and/or method of use of IRESSA™ (gefitinib) Tablets. This product is the subject of this new drug application for which approval is being sought.

(iii) US Patent No. 5,770,599

(a) Expiration Date:

April 26, 2016 (subject to change if the patent term is extended pursuant to 35 USC 156)

(b) Type of Patent:

US Patent No. 5,770,599 contains drug substance claims, pharmaceutical composition claims, and method of use claims.

(c) Name of Patent Owner(s):

Zeneca Limited
Macclesfield, Cheshire, England

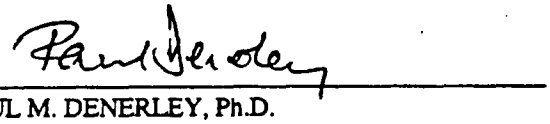
(d) Agent Authorized to Receive Notice:

The agent of the patent owner in the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and 21 CFR sections 314.52 and 314.95 is:

General Counsel
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

(e) Declaration:

The undersigned declares that US Patent No. 5,770,599 covers the formulation, composition, and/or method of use of IRESSA™ (gefitinib) Tablets. This product is the subject of this new drug application for which approval is being sought.



PAUL M. DENERLEY, Ph.D.

B. EXCLUSIVITY INFORMATION

Applicant claims an exclusivity period of five years from the date of approval of this New Drug Application pursuant to 21 CFR 314.108(b)(2). To the best of Applicant's knowledge or belief, a drug has not been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act which contains any active moiety in IRESSA™ (gefitinib) Tablets, the drug product for which Applicant is seeking approval.

EXCLUSIVITY SUMMARY for NDA # 21-399 SUPPL #

Trade Name IRESSA Generic Name gefitinib

Applicant Name AstraZeneca Pharmaceuticals HFD- 150

Approval Date 5-5-03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_✓_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_✓/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_✓/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Richard Pazdur
5/5/03 12:03:46 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-399 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 8-2-02 Action Date: 5-5-03

HFD-150 Trade and generic names/dosage form: IRESSA (gefitinib) tablets

Applicant: AstraZeneca Pharmaceuticals Therapeutic Class: 1P

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Iressa is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

Is there a full waiver for this indication (check one)?

✓Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
✓Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage_____
Max____ kg____ mo.____ yr.____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960

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

/s/

Amy Baird
5/5/03 12:02:15 PM

Demographic Worksheet

Application Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-399 Submission Type: N/A (pilot) Serial Number: N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	123	All Females	93	Females >50	69
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	0	17-64	124	≥65	92
Race:	White	196	Black	7	Asian	4
	Other	9				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?				Was gender-based analysis included in labeling?	
			If "No" is selected, indicate which applies or provide comment below		Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☐	☒

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☒ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was age-based analysis included in labeling?	
			If "No" is selected, indicate which applies or provide comment below		Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒ Sponsor ☒ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?				Was race-based analysis included in labeling?	
			If "No" is selected, indicate which applies or provide comment below		Yes	No
Efficacy	☐ Yes	☐ No	☒ Inadequate #'s	☐ Disease Absent	☐	☒
Safety	☐ Yes	☐ No	☒ Inadequate #'s	☐ Disease Absent	☐	☒

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

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

/s/

Grant Williams
10/16/02 06:51:40 AM

ITEM 16 - CERTIFICATION STATEMENT

Re: IRESSA NDA 21-399

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP, that we did not use and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b)

Sincerely,

Vice President, Regulatory Affairs

Division Director's Memorandum

Date: May 1, 2003
NDA: 21-399
Sponsor: AstraZeneca Pharmaceuticals (AZ)
Proprietary Name: IRESSA® (gefitinib, ZD1839) 250 mg tablets

Introduction: This submission is an NDA for the new molecular entity IRESSA® (gefitinib, ZD1839) proposed for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy and docetaxel (third-line indication). ZD1839 inhibits receptor tyrosine kinases, including the epidermal growth factor receptor-tyrosine kinase (EGFR-TK); however, the precise anticancer mechanism of action has not been established.

This application was reviewed as a Fast Track rolling submission with the first section submitted on July 30, 2001. The final section (CMC) was received on August 5, 2002. The PDUFA goal date for this priority review was February 5, 2002. After safety reports of pulmonary toxicity became available from the Japanese post-marketing experience in October, 2002, additional clinical information was requested by the FDA.. Major safety supplements concerning interstitial lung disease (ILD) were submitted on October 17, 2002, December 24, 2002 and January 17, 2003. These supplements resulted in goal date of May 5, 2003.

Chemistry/Manufacturing and Controls: See Dr. Liang's review for details.

.... AZ elected to produce the brown tablet for commercial supply.

The PAI was found acceptable by the Office of Compliance on November 19, 2002.

There are no CMC post-marketing commitments.

Preclinical:

Refer to Dr. McGuinn's primary review and Dr. Morse's team leader memo.

AstraZeneca proposed the drug be classified as a specific inhibitor of the EGFR-TK. The FDA pharmacology/toxicology reviewers noted that ZD1839 inhibited a variety of tyrosine kinases. No correlation had been demonstrated between EGFR levels and ZD1839 clinical response. The MOA section of labeling was edited to reflect this viewpoint.

There are no pre-clinical post-marketing commitments.

Biopharmaceutics: See Dr. Abraham's review.

ZD1839 tablets are 60% bioavailable and produce peak plasma levels 3-7 hours after dosing. Relative bioavailability is not significantly altered by food. Daily oral administration resulted in a 2-fold accumulation, reaching steady state concentration within 7-10 days. Absorption was decreased when gastric pH was increased by

administration of sodium bicarbonate. Gefitinib is cleared primarily by the liver and undergoes extensive hepatic metabolism, predominantly by cytochrome P450 3A4. Labeling precautions note an interaction with coumadin resulting in elevated INR levels and reports of bleeding from concomitant use of coumadin and Iressa.

Phase 4 biopharmaceutical commitments include the following two trials. The sponsor is required to submit the study and individual data for Trial 32 (Phase I study in Normal, Moderate and Severe Hepatic Impairment) to provide proper dosage adjustments in this population. A pharmacokinetic study is required in patients taking Iressa in combination with warfarin to explore the mechanism of interaction

Clinical and Biostatistical Reviews

The present marketing application is to support the use of Iressa as a monotherapy in the treatment of non-small cell carcinoma after treatment with a cisplatin-containing regimen (first-line treatment) and docetaxel (second-line treatment). There is currently no approved therapy for the treatment of this disease setting. No "off label" use of any cancer drug or combination has demonstrated consistent activity in this settng.

First-line chemotherapy regimens (no prior therapy for advanced/metastatic disease) for the treatment of non-small cell lung cancer have generally used "doublet chemotherapy" regimens. These doublet combinations have combined cisplatin (or carboplatin) with etoposide, vinorelbine, gemcitabine, docetaxel or taxol. These regimens have response rates of approximately 25-30% with about 35-50% of patients alive at 1-year.

Docetaxel (Taxotere) has been approved for the second-line treatment of non-small cell lung cancer (prior platinum-based chemotherapy). Two randomized trials were performed to support the application. An overall survival advantage was demonstrated in a trial comparing docetaxel to best supportive care (overall survival $p = 0.01$, 1-year survival 37% versus 12%, $p \leq 0.05$). Another randomized trial compared docetaxel to either vinorelbine or ifosphamide and demonstrated a survival trend favoring the docetaxel arm. The response rates for the docetaxel treatment was only 5.5% and 5.7% in the two trials.

Third-Line Indication

Refer to the medical officer review, medical team leader, and statistical reviews for a description of the third-line trials. The registration trial (Study 39) was a multi-center Phase 2 trial that randomized patients to either 250 or 500 mg of Iressa. The primary efficacy endpoints were objective response rate and symptom improvement rate. Of the 216 patients, 142 patients were refractory/intolerant to both platinum and docetaxel (third-line). Another trial (Study 16) was a multi-center phase 2 trial. Advanced non-small cell lung cancer patients were randomly allocated to either 250 or 500 mg of Iressa. This study did not include patients from the United States; a total of 102 Japanese patients and 106 non-Japanese patients were enrolled. Objective response rate was the primary endpoint.

The discussion below focuses on analyses of response rate in the third line patients in Study 39. The FDA reviewers and a consensus of the ODAC members believed that data regarding symptom improvement were interesting, but not evidence of definitive clinical benefit. This conclusion was based on the lack of a concurrent control arm, the unblinded nature of the evaluation, the uncontrolled use of concomitant supportive care medications, and the lack of prospective data validating a two-point difference in scales as a clinically meaningful difference (see Dr. Williams' discussion).

In Study 39, among the 142 third line patients, there were no significant differences in response rates between patients treated at the 250 and 500 mg dose level [13.6% (95% CI 6.4%, 24.3%) and 7.9% (95% CI 3.0, 16.4%)], and results from the two arms were pooled. Overall, for both doses, 15 of the 142 patients achieved response, for a response rate of 10.6% (95% CI, 6.0%, 16.8%). All responses were partial responses. The median duration of response was 7 months. Findings from Study 16 corroborate this observed response rate in the third-line setting. In the 35 patients who had progressive disease on a second line chemotherapy treatment, 4 patients (11%) had partial responses The results in the second line patients from Study 39 and from Study 16 also showed similar response rates.

The statistical review provides exploratory analyses of responding patients. (See Dr. Sridhara's Statistical review Addendum #1). An exploratory analysis of pooled data from the 250 and 500 mg levels in Study 39 revealed higher response rates in females compared to males (17.5% vs 5.1%) and non-smokers compared to smokers (29.4% versus 4.6%). These subgroup findings were also present examining individual dose levels and similar differences were seen both in second line patients of Study 39 and Study 16, which also noted a higher response rate for females (36%) compared to males (11.6%) in the whole study population. Reports of the expanded access program (table j) also noted studies demonstrating higher response rates in females and in non-smokers. Although the results of these subgroup findings are based on post-study explorations and cannot yet be considered definitive, their consistency across four distinct data sources (Study 39 third line and second line, Study 16, and expanded access data) is impressive. These differences will need to be further tested in randomized controlled trials. These findings will be provided in the product label.

First-Line Indication

The development program in non-small cell lung cancer included two large randomized, placebo-controlled trials examining doublet chemotherapy with or without the addition of Iressa (250 vs 500 mg). These trials enrolled chemotherapy naïve patients. Trial 14 used the doublet chemotherapy of gemcitabine plus cisplatin; Trial 17 used paclitaxel plus carboplatin.. Each trial failed to demonstrate an improvement in overall survival (primary study endpoint) with the addition of Iressa to the doublet chemotherapy. In addition, the secondary endpoints of progression–free survival and response rates were not improved by the addition of Iressa to the doublets.

Although AstraZeneca stated that these large trials were not performed to be the confirmatory trials (demonstration of clinical benefit) after the accelerated approval of Iressa, they clearly could have served that purpose had they not failed to show an effect. The Division has routinely allowed the demonstration of clinical benefit (e.g. improvement in survival) to be demonstrated in an earlier stage or less refractory population than the approval indication of accelerated approval drugs.

Expanded Access Program

AstraZeneca initiated an expanded access program in 2000. Over 20,000 patients have been entered on the program. The sponsor has provided the Agency with investigator's reports (meeting abstracts and publications) from institutions participating in the expanded access program (see Statistical Review, Table j). Combined data (excluding the Singapore site) noted a response rate of 6.5% (95% CI 4.9 to 8.5%). Responses in the expanded access program were more commonly noted in females, in non-smokers, in patients whose tumors were bronchioalveolar carcinomas. A small study from Singapore noted a relatively high response rate (38%, 95% CI 17.3, 64.3%) in 18 patients.

Toxicity Analysis

AstraZeneca presented data at the ODAC meeting summarizing safety data on Trial 39. The sponsor believed that the drug was generally well tolerated with predictable and manageable adverse events, primarily skin and gastrointestinal toxicities. There appeared to be no special population safety concerns and the drug appeared to be "nontoxic compared with cytotoxic chemotherapy."

The initial review of Iressa for the treatment of patients with NSCLC who are refractory to available therapy was completed on October 15, 2002 in anticipation of a FDA action in mid-October, 2002. However, reports of multiple ILD deaths from the Iressa post-marketing experience in Japan reported after the ODAC meeting, prompted the FDA to re-evaluate US toxicity databases and to review Japanese post-marketing data.

ILD is a complex disease, representing diverse entities that are described by investigators using different terms. (The sponsor captured cases by a collection of 24 MedDRA terms) A detailed analysis of the sponsor Drug Safety database was performed. This comprised 50,005 patients (including 18,960 from marketed use in Japan). Four hundred eight cases of ILD, 324 from Japan, and 84 from the US/rest of the world were identified. Median time to onset of ILD was 24 days in Japan and 42 days in the US experience. The reported rate in Japan was about six times the US reported rate.

Study 039, the primary efficacy study, which does not have a control arm does not suggest a high rate of ILD. There is only one report of ILD in 216 patients. Two cases of pneumonia were reported as adverse events. Other severe pulmonary events, considered by the investigator as related to disease, were also reported (pneumonia in 4, dyspnea in three, and apnea in two). Such events in a single-arm study of lung cancer patients

provide little useful information because of the high rate of such events in untreated patients.

To further evaluate ILD the safety database from the Iressa Expanded Access Protocol (EAP) and the safety database from two first-line NSCLC trials comparing chemotherapy (gemcitabine/cisplatin or carboplatin/paclitaxel) plus placebo to chemotherapy plus Iressa were examined. The ILD incidence was was comparable in the Iressa and placebo treatment arms (0.7%). A summary of the pulmonary adverse events from these studies is given below in a table excerpted from Dr. Cohen's review. Event rates are similar in each treatment arm and the placebo arm:

Incidence of ILD-type events from Phase III placebo-controlled combination therapy trials (0014 and 0017)

Event	**ZD1839 500 mg** (n=700)	**ZD1839 250 mg** (n=704)	**Placebo** (n=696)
ILD-type event	8(1.1)	8(1.1)	6(0.9)
Dyspnea	181(25.9)	189(26.8)	193(27.7)
Cough	146(20.9)	159(22.6)	148(21.3)
Pneumonia	45(6.4)	53(7.5)	48(6.9)

Thus the FDA evaluation reveals an overall ILD incidence of 0.94% (1.9% in Japan, 0.29% in EAP, 0.7% in first-line randomized trials). The incidence of fatal ILD is 0.31% (0.64% in Japan and 0.07% in the EAP). The reason(s) for the higher ILD incidence in Japan is unknown, but it does not appear related to under-reporting from any data source. In addition the incidence of ILD with Iressa treatment appears comparable to that seen with other chemotherapy drugs.

Please see Drs. Williams', Eugene Sullivan (FDA pulmonary Division), and Martin Cohen's reviews on ILD.

Recommendations, Post-marketing Commitments, Administrative Issues

The sponsor seeks marketing approval for a third-line NSCLC indication. Because of the failure to demonstrate any differences in the dosing arms of Iressa, Trial 39 is regarded as a single-arm treatment study pooling two dose levels. Approval under subpart H on the basis of single-arm trial using a response rate endpoint in a refractory disease setting has been previously accepted by the DODP. This strategy has led to the approval of most of

the oncology drugs approved under subpart H (e.g., capecitabine, irinotecan). The Agency has accepted response rates with a reasonable duration as a surrogate endpoint "reasonably likely" to predict clinical benefit.

The partial response rate demonstrated in this population was 10%, i.e., 15 of 142 patients (95%CI 6.0, 16.8), with a median response duration of 6 months. This response rate is based on partial responses noted in 15 of 142 patients. Complete responses were not observed. As noted in the statistical review, the response rate (point estimate) represents a lower level of activity than previously accepted in applications under consideration for subpart H. A similar response rate associated with an improvement in time to progression supported the accelerated approval of oxaliplatin for refractory colon cancer.

The magnitude and duration of response rates necessary to affect overall survival remains controversial. Survival prolongation may also be influenced by disease stabilization (or prolonged time to progression) that can not be adequately assessed in single-arm trials. Agents that are identified by response rate determinations in heavily pre-treated, refractory patients may have novel mechanisms of action that will lead to clinical benefit.

The irinotecan application in refractory second-line colorectal cancer (June,1996) also had a low response rate---a 15% response rate (95% CI 10%, 20%). Of the 193 patients, 23 PRs and 2 CRs were observed; the median response duration was 5.8 months. After accelerated approval, irinotecan was compared to either best supportive care or chemotherapy in refractory colon cancer and survival advantages were demonstrated with single-agent irinotecan. Single-agent irinotecan was associated with considerable toxicity with over 25% of patients hospitalized for drug-related toxicities and 1.6% of the study population experienced deaths which were "potentially drug related." In comparison to Iressa, irinotecan was approved in an earlier disease setting (second line), with a similar level of activity (response rates and duration), more grade 3-4 toxicities, and greater treatment-related death rates.

Responses to Iressa observed in Trial 39 tended to occur more frequently in women compared to men, in non-smokers compared to smokers, and in the adenocarcinoma histology compared to other histologies(see Dr. Sridhara's Stat Review Addendum #1). Responses were also were more frequent in non-Caucasians than in Caucasians. Study 16 found a higher response rate in Japanese patients than "non-Japanese" patients, and in females, similar to findings in Study 39. There is no apparent explanation for these observations. Previous experience with lung cancer trials do not provide a precedent for these subgroup findings. Labeling of the drug will note these observations. Additional post-approval trials have been designed to prospectively examine these observations

Complicating the review of this application was the emergence of first-line data (Trials 14 and 17). These large, randomized trials failed to demonstrate any improvement in response rate, time to progression, or survival with the addition of Iressa to commonly used doublet chemotherapy regimens. If successful, these trials would have been appropriate to confirm clinical benefit for Iressa. Conventional cytotoxic drugs generally

have higher response rates in less heavily pretreated patients; hence, response rates would have been expected to exceed those noted in the approval indication.

On September 24 2002, the Oncology Drugs Advisory Committee (ODAC) met and discussed the current NDA. The committee supported the approval of Iressa for the third-line treatment of NSCLC. The response rate and duration in the third-line setting was considered reasonably likely to predict clinical benefit. The committee believed that the disappointing results of the first-line trials should not prevent approval for the third-line indication approval.In particular the results of the first-line studies did not test response as a surrogate for survival because the addition of Iressa to chemotherapy in the first-line treatment did not significantly affect the surrogate outcome in either first-line trial. Explanations for the discordant efficacy findings between the refractory and chemotherapy-naïve patients included the following.

- Iressa might suppress tumor growth and abrogate conventional chemotherapy's cytotoxicity on rapidly proliferating cancer cells. This explanation is supported by recent data failing to show benefit for the addition of tamoxifen to chemotherapy in adjuvant breast cancer trials.
- Initial treatment with chemotherapy might induce metabolism of EGFR(TK) or other kinases requisite for subsequent tumor response to Iressa.
- Third-line patients may represent a select subgroup of patients who are susceptible to Iressa.
- The addition of a third chemotherapy agent to NSCLC doublet chemotherapy has not provided additional benefit in previous chemotherapy trials in the literature. The results of the addition of Iressa to conventional combination chemotherapy may simply corroborate these prior reported experiences.

It is appreciated that none of these possible explanations is supported by any data. What remains true, however, is that across both second and third line patients in Study 39, Study 16, and the expanded access experience, a low, but real, response rate was observed.

The applicant has committed to perform the following randomized trials:

1. **Subpart H:** Randomized phase 3 survival study comparing Iressa plus best supportive care (BSC) versus placebo and BSC in NSCLC patients who have received one or two prior regimens.
2. **Subpart H**: Phase 3 trial of Iressa Versus Taxotere in NSCLC patients who have received first-line treatment and have recurrent or progressive disease
3. **Subpart H**: Placebo controlled symptom improvement study in refractory symptomatic stage 3 or 4 NSCLC. Symptom improvement will be the primary endpoint.
4. BR 19 (NCIC, EORTC): Phase III prospective randomized placebo controlled trial of Iressa in completely resected Stage I, II, IIIA NSCLC patients
5. SWOG 0023: Randomized double blind placebo-controlled trial of cisplatin/etoposide/radiotherapy with consolidation docetaxel followed by maintenance therapy with Iressa or placebo in patients with inoperable Stage II NSCLC

These studies are adequate to evaluate the potential Iressa clinical benefit in NSCLC. Completion of these trials seems feasible. Two trials are sponsored by cooperative oncology groups and are presently enrolling patients. Approval of Iressa would not substantially effect patient accrual since the trials are either in an earlier treatment phase/disease stage than the approved indication or are being conducted outside of the United States.

In summary, I concur with the ODAC that the response rate and duration in Study 39among third line patients is reasonably likely to predict clinical benefit. The risk-benefit relationship demonstrated for Iressa is acceptable and similar to previous approvals for oncology drugs under subpart H. Several of these drugs have already demonstrated clinical benefit in post-approval trials. Response rates in the second line subset of study 39 and in study 016 provide additional assurance of Iressa's activity in NSCLC. Iressa, in general, appears well tolerated with predictable and manageable adverse events, primarily skin and gastrointestinal toxicities, but with one specific serious toxicity . Review of interstitial lung disease (ILD) with Iressa indicated that the frequency of ILD is approximately 1%. Clinical experience with approved oncology drugs has documented similar or higher levels of life-threatening toxicities. Phase 4 commitments appear adequate and achievable.

Labeling issues:

The Division has suggested a change in the proposed indication to restrict approval to treatment of patients as follows:

> IRESSA is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

Labeling includes data and warnings regarding interstitial lung disease as well as information about the different response rates seen in subset analyses (lower response rates in men, smokers, histologies other than adenocarcinoma).

Data Integrity Issues: See Clinical Inspection Summary by Dr. U. Two US sites (Pippen, Osborne) and a European site (Albano) were audited by DSI, and were found to be acceptable with regard to data integrity supporting safety and efficacy. Over 90% of the investigators responded to the financial disclosure request. Three investigators out of 1077 in the phase 3 randomized studies admitted to having received significant payments from the Applicant. It is unlikely that financial conflict of interest played a significant role in study results given the large number of investigators and multi-center accrual pattern.

Tradename consultation:

DMETS recommended rejecting the tradename, Iressa® ,because of potential confusion with the Alesse®, an oral contraceptive. AZ noted that Alesse was generally prescribed by Obstetricians and Gynecologists rather than oncologists, and tablets were dissimilar in

size, shape and milligram content. Contraceptives are prescribed in distinctive 28-day dispensers. In an October 11 teleconference between DODP and DMETS, Carol Holquist of DMETS agreed that it would be reasonable to allow the name Iressa® with an AZ commitment to collect data on medication errors. An updated review by DMETS on April 24, 2003 suggests potential confusion between Evista (raloxifene) and Iressa. Evista is primarily prescribed by gynecologists and primary care physicians. Patients are usually given starter kits and are familiar with the medication prior to obtaining the first pharmacy-filled prescription. The Division has allowed AZ to proceed with the tradename Iressa with a plan for collection of post-marketing drug errors. This plan will require the sponsor to submit reports of all medication errors, both potential and actual, that occur within the United States with Iressa for two years following the date of approval.

Pediatric Considerations: The Applicant was granted a waiver of the Pediatric Rule. Non-small cell lung cancer does not occur in children.

Richard Pazdur, MD

Director, Division of Oncology Drug Products

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Richard Pazdur
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MEDICAL OFFICER

NDA Team Leader Review #1

Application: NDA 21-399
Drug: ZD1839 (IRESSA)
Review date: 3/28/03

Introduction

This second team leader review incorporates all of the information discussed in team leader review #1 plus updated analyses of interstitial lung disease (ILD) observed after ZD1839 treatment. The initial review was completed on October 15, 2002, in anticipation of an FDA action in mid-October. However, reports of multiple deaths from the ZD1839 post-marketing experience in Japan prompted FDA to re-evaluate US toxicity databases and review the Japanese data on ILD before taking an action. FDA asked for comprehensive analyses of the world-wide experience and submission of complete data on the ILD events. FDA also consulted with the Japanese authorities. After review of these data, although we cannot give a precise value for the ILD risk, we can outline the limits of that risk, and we can now make a reasonable determination of benefit versus risk of ZD1839 treatment in patients with nonsmall cell lung cancer that is refractory to available therapy.

This review includes a regulatory background, discussion of study results, deliberations of the ODAC, phase 4 post-marketing commitments, and a review of ILD reported after treatment with ZD1839.

AstraZeneca submitted a marketing application intended to support accelerated approval for third-line treatment of non-small cell carcinoma (NSCLC). Prior to the Agency's action on this application, results became available from ZD1839 studies in the first-line treatment of NSCLC. Two large randomized trials failed to show clinical benefit from the addition of ZD1839 to standard first-line cisplatin-based regimens. The Agency had expected that if ZD1839 received accelerated approval in refractory NSCLC, these trials would provide the post-approval evidence of ZD1839 clinical benefit necessary for conversion to regular approval status. Given the lack of ZD1839 clinical benefit in patients with previously untreated NSCLC, a dilemma for reviewers was whether a 10% response rate in a 3rd line treatment is reasonably likely to predict clinical benefit.

The New Drug Application (NDA) efficacy results consist of tumor response rate data, supported by QOL and symptoms data, in non-small cell lung canceer (NSCLC) patients who have no available therapy, intended to fulfill FDA's requirements for *accelerated approval*. In the following paragraphs FDA's requirements for *accelerated approval* and *regular approval* of new drugs are discussed.

Regulatory background: regular approval versus accelerated approval

Regular marketing approval of oncology drugs requires substantial evidence of efficacy from well-controlled clinical trials. Guidance promulgated in the 1980's indicated that efficacy should be demonstrated by prolongation of life, a better life, or an established surrogate for at least one of these. In 1992 Subpart H was added to the NDA regulations to allow *accelerated approval* (AA) for diseases that are *serious or life-threatening* where the new drug appears to provide *benefit over available therapy*. AA can be granted on the basis of a *surrogate endpoint* that is *reasonably likely to predict clinical benefit*, an explicitly lower strength surrogate than would be a basis for regular approval. After AA, the applicant is required to perform a post-marketing study to demonstrate that treatment with the drug is indeed associated with clinical benefit. If the post-marketing study fails to demonstrate clinical benefit or if the applicant does not show *due diligence* in conducting the required study, the regulations describe a process for rapidly removing the drug from the market.

Under AA, tumor response has been used as a surrogate *reasonably likely* to predict clinical benefit for ten oncology drug accelerated approvals:

Oncology drug accelerated approvals based on tumor response

Drug	Indication
Liposomal doxorubicin	Kaposi's sarcoma, second line
Docetaxel	Breast cancer, second line
Irinotecan	Colon cancer, second line
Capecitabine	Breast cancer, refractory
Liposomal cytarabine	Lymphomatis meningitis
Temozolomide	Anaplastic astrocytoma, refractory
Liposomal doxorubicin	Ovarian cancer, refractory
Gemtuzumab ozogamicin	AML, second line, elderly
Imatinib mesylate	CML, blast phase, accel. phase & failing interferon
Oxaliplatin	Colon cancer after failing bolus 5FU/LV and camptosar

Evaluation of the ZD1839 data in a regulatory context

As outlined by Dr. Cohen, the applicant's efficacy claim is based on a 10% FDA-verified partial response rate in 139 patients with refractory NSCLC and the applicant's findings of improvements in cancer related symptoms and improvement in quality of life. (These latter findings would be evidence of clinical benefit, not an effect on a surrogate.)

These responses have been subject to an unprecedented level of validation. FDA obtained the scans and each response was validated by a consultant radiologist. A recent update showed the median duration of response to be six months, measured from the data of first response.

Response rate results from third-line treatment

Is a 10% response rate of six months duration documented in 139 patients sufficient to support AA in refractory NSCLC for a drug that, compared to many cytotoxic anticancer agents, is relatively nontoxic? Low response rates have been predictive of clinical benefit in some settings. Irinotecan received in the treatment of refractory colon cancer based on a relatively low response rate and subsequently demonstrated a survival benefit both in the refractory and the first-line settings.

Preliminary results from first-line treatment

Recently the applicant provided FDA with preliminary analyses of two trials evaluating standard chemotherapy plus or minus ZD1839 in first-line treatment of NSCLC. Despite about 350 patients per arm and adequate follow-up (about 240 events per arm) neither showed a survival benefit for ZD1339.

Study 14 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	365	243	9.9	44%
250 mg ZD1839	365	248	9.9	42%
Placebo	363	236	11.1	45%

Study 17 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	347	246	8.7	38%
250 mg ZD1839	345	232	9.8	42%
Placebo	345	247	9.9	42%

Similarly there was no improvement in response rate:

	Study 14 Response Rate	**Study 17 Response Rate**
500 mg ZD1839	49.7%	32.1%
250 mg ZD1839	50.1%	35.0%
Placebo	44.8%	33.6%

Even though these data were generated in the first-line NSCLC treatment setting, they are important for our determination of ZD1839 efficacy in treating refractory NSCLC. Accelerated approval based on the surrogate endpoint of tumor response in the refractory setting has often been followed by clinical trials in first- or second-line treatment settings intending to demonstrate a survival benefit or some other clinical benefit. The FDA oncology group has never received an application for accelerated approval in refractory patients when definitive data in another related setting, such as first line treatment, show a lack of efficacy.

Tumor Symptom and QOL data from third-line treatment

What are the meaning of the analyses of tumor symptoms and QOL in the context of a single arm open study? The applicant has done a thorough job of evaluating symptomatic changes, but uncertainty regarding the meaning of these data cannot easily be resolved without a blinded study with a concurrent control arm. The applicant claims clinical benefit is demonstrated by individuals showing a 28-day, 2-point improvement on the 28-point Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L). The 2-point threshold is based on studies showing that a 2-3 point LCS change in study populations is correlated with changes in performance status, weight loss, and TTP. The applicant finds that about 40% of patients in Study 39 derive such benefit, and that the benefit correlates with response and survival. For instance, the rate of a 2-point response on the LCS was 96% for objective tumor responders, 71% for stable disease patients, and 17% for progressors.

There are fundamental problems with the applicant's symptom benefit claims. Without a concurrent control arm, we cannot know whether these symptom results might not be entirely from placebo effect, from hope associated with starting a promising

investigational cancer drug. While a 2-point difference on the LCS determined in study populations may have some meaning in a randomized study, there are no data validating its use as an efficacy endpoint for individuals in a single-arm study. Alternatively, as noted by Dr. Cohen, some symptom improvement could be attributed to concomitant medications given to ameliorate these symptoms; or, in patients recently stopping chemotherapy, symptom improvement might occur with recovery from chemotherapy toxicity.

A correlation of positive symptom findings with response rate would not be unexpected. One might expect that responders would feel better after being informed of their tumor status. Certainly some analytical bias would be expected; for instance, patients going off study early because of tumor progression might not provide sufficient data for the required 28-day verification of symptom response. Therefore, early progressors could not be symptom responders. The 2-point LCS response associations with tumor response and with survival could be due to shared prognostic factors, e.g., prognostic factors (known or unkown) for response, tumor symptom improvement, and survival may be similar. Rather than causing symptom improvement or survival prolongation, tumor response might merely be associated with symptom changes and longer survival through shared baseline prognostic factors.

In the final analysis, it is unclear that the changes observed on the LCS symptom scale represent significant clinical benefit and that the changes observed can be confidently ascribed to ZD1839 treatment. A randomized, blinded trial will be required to make this determination. Although such data might enter into one's judgement whether a 10% response rate is reasonably likely to predict clinical benefit in the refractory NSCLC setting, they clearly are not sufficient for a clinical benefit claim for full NDA approval.

Deliberations of the Oncologic Drugs Advisory Committee

On September 24, 2002, the ZD1839 NDA results were discussed before the Oncologic Drugs Advisory Committee (ODAC). At the open public hearing, a number of patients treated with ZD1839 on the expanded access protocol presented their anecdotal positive experiences. After applicant and FDA presentations, the ODAC addressed the following questions:

Questions to the Committee:

1. The FDA believes the relevance of the symptom improvement data discussed above cannot be adequately evaluated without a randomized, blinded study with an adequate control arm (the two doses of ZD1839 show no difference in efficacy and are thus not adequate). Do you agree?

   YES – 9 NO – 5

   The Committee felt that the data were supportive, but not definitive, given the lack of a blinded control arm.

2. Given the lack of clinical benefit in two large studies of ZD1839 in combination with standard first-line NSCLC chemotherapy, is the Study 0039 response rate of 10% in 139 patients with resistant or refractory NSCLC reasonably likely to predict ZD1839 clinical benefit in NSCLC?

   YES – 11 NO – 3

It was clear from the discussion that most ODAC members did not see a necessary connection between clinical benefit in the first-line combination setting and the third-line treatment setting. Committee members did cite examples of agents with a cytostatic mechanism of action appearing to inhibit the beneficial effects of chemotherapy.

Interstitial Lung Disease (ILD)

Please refer to Dr. Cohen's primary review and Dr. Eugene Sullivan's pulmonary consultation for details about the interstitial lung disease (ILD) findings. ILD has been reported with ZD1839 treatment in the both US and Japan, with recently increasing rates, probably because of increased investigator awareness. The reported rate in Japan is about six times the US reported rate. ILD is a complex disease, representing a number of different entities that are described by investigators using many different terms. (The sponsor captured cases for evaluation by a collection of 24 MedDRA terms.) The clinical syndrome described with ZD1839 is that of the Acute Respiratory Distress Syndrome, with the acute onset of rapidly progressing dyspnea associated with diffuse interstitial/ground glass opacities by high resolution CT, negative bacterial cultures, and a histologic pattern termed diffuse alveolar damage.

The collection of toxicity findings as described in the next paragraphs are perplexing:

- The rate reported from Japan is much higher than in the US
- There was no increase in the incidence of ILD in the placebo-controlled studies of ZD1839 given in combination with cytotoxic chemotherapy

A detailed analysis was performed on a database with a cutoff date of December 11, 2002, including a total of 50,005 patients (including 18,960 from marketed us in Japan). This included 408 cases of ILD, 324 from Japan, and 84 from the US/rest of world. As shown below, median onset to ILD was 24 days in Japan and 42 days in the US experience. Demographics are given below. For the US experience, the demographics appear similar to the population with lung cancer, affecting men and women nearly equally.

Characteristic	Japan	US/Rest of World
Median age	67	63
Sex Male Female	 79% 17%	 56% 44%
Median onset (days)	24	42

Fifty seven percent of patients had previously received chemotherapy and thirty one percent had previously received radiation therapy. In fatal cases, death generally occurred 1-2 weeks after onset.

ILD in the Expanded Access Protocol (EAP)

The reported ILD rate in the EAP is much lower than the rate reported from the Japanese post-marketing experience. One possibility is that Japan and the EAP have similar ILD rates but the reporting rate is lower in the EAP than in Japan. AZ was asked to describe the EAP adverse reaction reporting procedures. AZ personell perform monthly monitoring calls to remind investigators about SAE reporting requirements. The contract resarch organization monitors SAE reporting at each site and recommends site visits if a site displays a decreased number of reports. When patients withdraw from the EAP, the reason for withdrawal must be documented as either progressive disease or AE. If the description of AE is pulmonary in nature, the site is queried with a special questionnaire evaluating the possibility of ILD (begun August-September, 2002). After withdrawal, patients are to be followed up for 30 days for resolution of all AEs. All deaths occurring within the trial period or within 30 days after last dose are to be reported to AZ.

It is interesting to compare the Japanese post marketing reports and the US EAP reports. Overall, the reporting rate was higher for SAEs from the US than from Japan as shown in the following table:

	# patients	# patients with SAEs	% reporting rate
US EAP	19,612	2,149	11.0%
Japan	21,567	642	3.0%
Clinical Trials	4,276	1,225	28.6%

However, the proportion of reported SAEs that were due to ILD was much higher in Japan than in the US or in clinical trials:

	Percent of SAEs that were from ILD
US EAP	1.7% (62/3609)
Japan	48.9% (398/814)
Clinical Trials	0.7% (20/2780)

Reviewer comment:
There is no clear explanation for the different rate of reported ILD events from the Japanese post marketing experience and the US EAP. The procedures used by AZ to collect information on SAEs on the EAP seem reasonable, and I see no reason to expect that this system would have a lower capture rate for SAEs than even a rigorous post-marketing detection system. The EAP AE report rate was much higher than the Japanese rate (11% versus 3%), suggesting that the EAP AE capture rate was adequate. Although the EAP SAE report rate was less than the rate reported in clinical trials, most patients in these clinical trials received combination chemotherapy and would be expected to have a higher rate of SAE reports.

ILD in placebo controlled trials of ZD1839 plus chemotherapy

The INTACT 1 and INTACT 2 trials compared chemotherapy (gemcitabine/cisplatin or carboplatin/taxol) plus placebo to chemotherapy plus ZD1839. The ILD rate was nearly identical with and without ZD1839 (16/1404 or 1.1% for ZD1839 versus 6/696 or 0.9% for placebo). Similarly, there was no increase in any of a variety of pulmonary symptoms in the ZD1839 arm. One possibility for the lack of ZD1839 ILD in these studies is that chemotherapy abrogated the ZD1839 pulmonary toxicity. However, other ZD1839 toxicities were not abrogated by chemotherapy: the the incidences of expected toxicities of rash and diarrhea were increased in the ZD1839 plus chemotherapy arms.

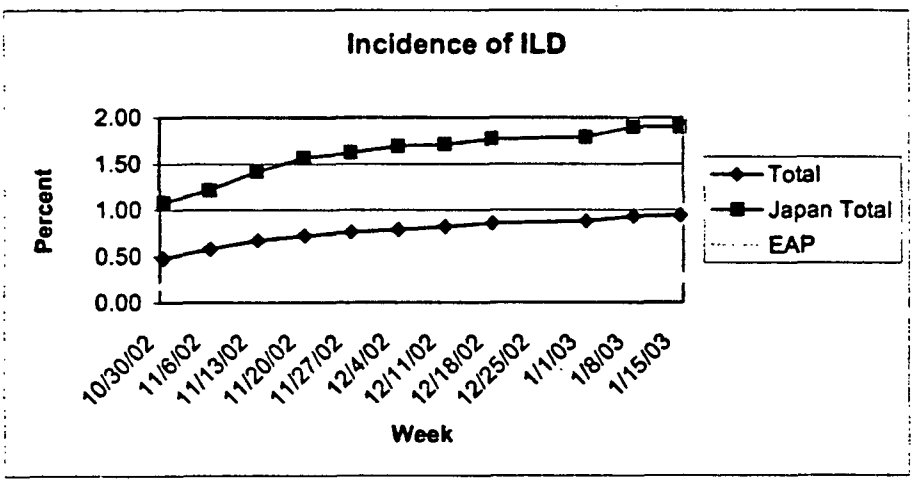
ILD reports and ILD deaths worldwide over time

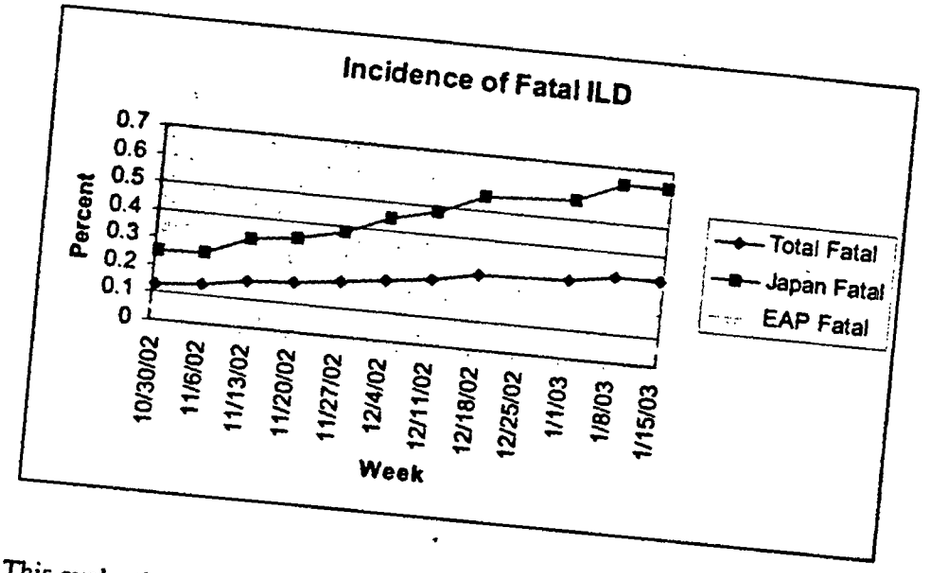
A total of 533 cases are described in the submitted data with a data cutoff of January 8, 2003. The incidence of ILD and fatal ILD are described in the following tables and graphs.

	ILD events/Patient Exposure (N) as of 10/11/02	ILD events/Patient Exposure (N) as of 1/13/03
EAP	28 / 16,000	63 / 19,760
Compassionate Use	14 / 6,000	24 / 8,164
Japanes Post-marketing	41 / 10,000	446 / 21990

INCIDENCES (PERCENT) OF ILD AND FATAL ILD

Date	Total	Total Fatal	Japan Total	Japan Fatal	EAP Total	EAP Fatal
10/30/02	0.48	0.13	1.08	0.25	0.21	0.06
11/6/02	0.58	0.14	1.21	0.26	0.21	0.06
11/13/02	0.67	0.17	1.41	0.32	0.22	0.06
11/20/02	0.72	0.18	1.56	0.34	0.22	0.06
11/27/02	0.76	0.2	1.62	0.38	0.23	0.07
12/4/02	0.79	0.22	1.69	0.44	0.24	0.07
12/11/02	0.82	0.24	1.71	0.48	0.26	0.06
12/18/02	0.86	0.27	1.77	0.55	0.28	0.07
1/1/03	0.88	0.28	1.79	0.57	0.29	0.07
1/8/03	0.93	0.31	1.9	0.64	0.29	0.07
1/15/03	0.94	0.31	1.9	0.64	0.29	0.07





This evaluation of ILD reveals an overall incidence of 0.94% (1.9% in Japan and 0.29 in EAP). The incidence of fatal ILD is 0.31% (0.64% in Japan and 0.07% in the EAP). The incidence increased in all settings after investigators became aware of the ILD danger. The reported death rate in the EAP did not increase, but remained about 0.07%.

Conclusions regarding ILD

It is not clear whether the higher rate of ILD events reported from Japan is due to genetic/cultural differences between the Japanese and US populations or from differences in AE reporting practices. A couple of factors suggest that under-reporting from the EAP is not responsible for the difference. First, the EAP had a much higher rate of reporting of non-ILD AEs than the Japanese experience. Second, ILD was not increased in the US placebo controlled studies. Although incidence rates seem to have increased after initial reports, the rates seem to be leveling off, and the US EAP rates remain less than one fifth of the Japanese rates. Reported US ILD deaths have not increased.

However, until we have controlled study data in this treatment setting (treatment of refractory NSLC with ZD1839 alone), we should be conservative in describing the ILD toxicity rate. Because this drug is the first oral drug for treating NSCLC, patients may assume that ZD1839 is nontoxic.

I recommend citing the worldwide ILD rate (about 1%) and noting that about a third of the ILD patients die. I would cite the higher rates reported in Japan (about 2%) and state that we do not know whether the increased Japanese rate is due to genetic/cultural factors or due to differences in reporting practices.

Discussion of overall benefit versus risk

The ODAC supported FDA's position that the symptom benefit data could not be adequately assessed without a concurrent control arm. These data will not be discussed further.

Whether the 10% response rate with a six-month response duration in NSCLC is reasonably likely to predict clinical benefit is the critical point for discussion. Clearly, response rates of a similar magnitude in some other tumors, such as metastatic colon cancer, have correctly predicted subsequent clinical benefit and have been the basis for accelerated approval. Obviously this is a judgement based on scientific knowledge and experience, and we must consider all available evidence. In this case, we also have an unprecedented additional consideration. We have two large randomized studies of excellent design that show no benefit for ZD1839 added to chemotherapy in first-line treatment of non-small cell lung cancer. Ironically, had ZD1839 already received accelerated approval, these studies would have served as phase IV post-marketing commitment studies to verify its clinical benefit. Now that these results have become available prior to a regulatory decision, we must weigh the significance of these negative findings on the accelerated approval process.

I believe these issues are in the realm of scientific and clinical judgement as intended by the writers of the 1992 accelerated approval rule. The AA requirements reflect both rigor and judgement, rigor in the demand for substantial evidence from adequate and well-controlled clinical trials, and judgement in what constitutes a surrogate reasonably likely to predict clinical benefit. The ODAC represents an appropriate forum for obtaining scientific and clinical judgement, and the ODAC clearly advised that despite the first-line trials showing no survival benefit, clinical benefit in the third-line setting was reasonably likely. The ODAC advice reinforces my pre-existing clinical opinion that these data are reasonably likely to predict clinical benefit.

Data from the first-line trials cannot address whether response rate is an adequate surrogate because the addition of ZD1839 to chemotherapy in first-line treatment did not significantly affect the surrogate outcome (response rate) in either of the 1000 patient first-line trials. This contrasts with the single-agent ZD1839 response rates of 10% and 20% in the third-line and second-line settings, respectively. While these results may seem puzzling, the conclusion is not in doubt: there was clear activity in the second and third-line trials, and there was clearly no additional activity when ZD1839 was added chemotherapy in the first-line setting.

While I can give no definitive explanation why ZD1839 did not demonstrate additional activity beyond that of chemotherapy in the first-line setting, one can certainly conjure up several plausible explanations:

- Perhaps only a subgroup of patients is destined to respond to first-line treatment, whether the treatment is cytoxic chemotherapy or is ZD1839.

Doublet chemotherapy may have extracted whatever benefit will occur in this setting. A third agent may not be beneficial, whether that agent is a third chemotherapy agent or ZD1830. Note that although numerous doublet chemotherapy regimens have demonstrated efficacy in the first-line setting, no triplet regimen has demonstrated additional efficacy.

- There could be a pharmacodynamic interaction between chemotherapy and ZD1839 in the first-line treatment setting (although there are no data suggesting this from preclinical studies): ZD1839 could suppress tumor growth and thus protect tumor from the effects of chemotherapy. This explanation is supported by recent data suggesting interactions between hormonal agents (e.g., tamoxifen) and chemotherapy. For example, recent results reported at the May, 2002 meeting of the American Society of Clinical Oncology suggest that simultaneous administration of adjuvant chemotherapy and tamoxifen was less effective than tandom use of these agents; disease-free survival was 67%, 62%, and 55% for tandom use, simultaneous use, and tamoxifen alone, respectively.

- Earlier treatment with chemotherapy could induce EGFR(TK) or other kinases that subsequently lend the tumor responsive to ZD1839 treatment in second-line or third-line settings.

- Third-line patients may represent a select subgroup of patients who are susceptible to ZD1839.

The final point is whether the benefits outweigh the risks of ZD1839, especially considering the risk of ILD. Even assuming the worst case scenario, that the US ILD rate is similar to the Japanese rate (2%) and that the fatal ILD rate is similar to the Japanese rate (0.64%), risks of this magnitude are commonly accepted in the treatment of NSCLC. (For reasons discussed above, I believe the ILD rate in the US EAP is actually lower than the rate reported from Japan.) This risk of ILD is similar to that seen with chemotherapy regimens for first-line and second-line treatment of NSCLC. In the INTACT 1 and INTACT 2 trials that included combination chemotherapy, a 1% ILD rate was noted in patients on the placebo arm. When one considers the high rate of morbidity that patients experience when treated with other available treatments for NSCLC, I believe the 'reasonably likely' benefit from a 10% response rate with ZD1839 from an oral agent with otherwise minimal toxicity would outweigh the risk of ILD toxicity.

Phase IV Commitments

It may seem premature to discuss phase 4 commitments prior to giving a recommendation; however, phase 4 commitments are an integral part of an AA recommendation. It is conceivable that because of drug approval, clinical trials to establish clinical benefit could not be conducted. In such a circumstance, accelerated approval could not be granted.

The applicant has outlined 5 clinical trials that will be conducted as phase IV commitments under Subpart H. These are described in the following table from Dr. Cohen's review:

Study type	Study pts.	Design	1^0 endpoint	2^0 endpoint	# patients	Complete date
Adjuvant	Stage IB, II, III Resected	Double-blind Placebo control	OS	DFS	1160	2007
Maintenance	Stage III Inoperable	Double-blind Placebo control	OS & PFS	–	840	2006
First-line	Stage III/IV PS 2-3 LCS ≤20 Medical conditions	Double-blind BSC control	Symptom improvement	OS TTP	207	2006
2nd or 3rd line	Stage III/IV PS 0-3	Double-blind BSC control	OS	PFS Symptoms	624	2006
2nd or 3rd line	Stage III/IV PS 0-2 LCS ≤20	Double-blind BSC control	Symptom improvement	OS TTP	207	2006

BSC=best supportive care; DFS=disease free survival; LCS= Lung cancer subscale; PFS=progression free survival; PS=performance status; OS=overall survival

Collectively, the studies evaluate potential ZD1839 clinical benefit in almost every remaining clinical setting. A survival advantage will be sought for adjuvant therapy following initial diagnosis and for maintenance therapy after optimal treatment of stage III lung cancer. In poor performance status patients, who generally do not tolerate combination chemotherapy, a placebo-controlled study will evaluate lung cancer symptoms on the LCS scale. In patients with refractory lung cancer, two placebo controlled studies at non-U.S. sites will be done. One will enter 624 patients and target survival. The other will enter 207 patients and target lung cancer symptoms.

Reviewer comment: The Division met with the applicant and found that these studies would provide sufficient evidence to determine whether ZD1839 provides clinical benefit in NSCLC. Clearly the adjuvant and maintenance studies will be performed, as they are ongoing cooperative group studies. The other studies will be done at non-U.S. sites, where ZD1839 will not be marketed and where use of a placebo (plus best supportive care) arm will be feasible. The three studies with a survival endpoint clearly have the potential to support regular approval. The two studies evaluating symptoms could provide sufficient evidence of clinical benefit if supported by response rates and time to progression advantages. Given the complexity of the various data, other demonstration of a survival advantage, it is not possible to specify exactly what set of such findings would support conversion to regular approval. The applicant could improve the design of the two trials designed to evaluate lung cancer symptoms by increasing the sample size to provide sufficient power to evaluate TTP (This point will be communicated to the applicant).

The exact design of the trial in a population with chemotherapy-resistant disease and intended to demonstrate a survival advantage (the fourth trial listed above) is still being

negotiated between FDA and the sponsor. FDA has recommended an "enrichment" study that targets a NSCLC sub-population with a higher response rate (e.g., adenocarcinoma patients). All NSCLC patients would be treated, but the primary analysis would be performed in the "enriched" population with adenocarcinoma.

Additional recommendations for phase 4 requirements

Recommendations

I recommend approval of IRESSA® (ZD1839, gefitinib) under Subpart H (accelerated approval) for patients with non-small cell lung cancer that has failed both platinum-based and docetaxel chemotherapies. The five studies discussed are acceptable Subpart H post-marketing commitments. In addition, the sponsor should perform pharmacogenomic studies as noted above. Completion of these studies according to the schedule provided by the applicant would indicate "due diligence" as required under Subpart H regulations.

GS

Grant Williams
Deputy Division Director
Division of Oncology Drug Products

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/s/

Grant Williams
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