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1 Executive Summary

1.1 Introduction

AstraZeneca has submitted NDA 206,995 for gefinitib for the treatment of patients with metastatic non-small lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Gefitinib is a tyrosine kinase inhibitor with activity against the epidermal growth factor receptor (EGFR) and some mutations in the receptor (exon 19 deletions or exon 21 L858R mutations). In in vitro assays, gefitinib also inhibited IGF and PDGF-mediated signaling.

All nonclinical toxicology studies required to support the approval of gefitinib were previously reviewed under NDA 21,399. The Applicant has submitted limited new pharmacology studies to support the mechanism of action of gefitinib in the intended patient population.

1.2 Brief Discussion of Nonclinical Findings

The Applicant presented data from the scientific literature identifying and characterizing sensitizing mutations in the intracellular kinase domain of epidermal growth factor receptor (EGFR) in tumor tissue samples obtained from a subset of patients with non-small cell lung cancer (NSCLC) who showed marked responses to gefitinib. The most common of these mutations were a set of deletions within exon 19 (’Ex19 del’) and a point mutation of exon 21 (’L858R’). The same studies suggested that EGF-induced activation of mutant EGFRs is enhanced and prolonged compared to the wild-type receptor. Gefitinib was able to inhibit EGF-induced autophosphorylation of mutant receptors (IC50=15 nM) at lower concentrations than wild-type receptors (IC50=100 nM). The data also demonstrated that inhibition of L858R EGFR phosphorylation inhibited the phosphorylation of known downstream targets of EGFR such as ERK1/2 and AKT.

In vivo data using NCI-H3255 L858R or the PC9 Ex19del cell lines in mouse xenograft models showed gefitinib-mediated inhibition of tumor growth and tumor regression. EGFR wild-type cell lines were not included in the currently submitted xenograft studies, however, data previously reviewed under NDA 21,399 showed that at gefitinib doses of 12.5 and 50 mg/kg, tumor volumes in A549-bearing nude mice were inhibited by 44% and ≤76%, respectively, without mention of tumor regression. Thus current in vivo data support the in vitro findings of higher sensitivity to gefitinib in tumors with selected EGFR mutations.

The pharmacology data support the proposed mechanism of enhanced gefitinib sensitivity in a subset of NSCLC patients carrying the EGFR point mutations in exons 18 and 21 or EGFR deletions in exons 19.
1.3 Recommendations

1.3.1 Approvability

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of gefitinib for the treatment of patients with metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

<table>
<thead>
<tr>
<th>The Applicant Proposes</th>
<th>FDA Recommends</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRESSA is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. (1)</td>
<td>IRESSA is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation as detected by an FDA-approved test [see Clinical Studies (14)]</td>
<td>The EPC is kinase inhibitor not tyrosine kinase inhibitor. Limitation of use is based on exclusion criteria in clinical studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have</td>
</tr>
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8.1 Pregnancy

Risk Summary

IRESSA can cause fetal harm when administered to a pregnant woman. Changed to conform to PLLR
of the potential hazard to the fetus or potential risk for loss of the pregnancy.

**Animal Data**

A single dose study in rats showed that gefitinib crosses the placenta after an oral dose of 5 mg/kg (30 mg/m², about 0.2 times the recommended human dose on a mg/m² basis). When pregnant rats were treated with ≥5 mg/kg from the beginning of organogenesis to the end of weaning there was a reduction in the number of offspring born alive. This effect was more severe at 20 mg/kg (approximately the human clinical dose on a mg/m² basis) and was accompanied by high neonatal mortality soon after parturition. In rabbits, a dose of 20 mg/kg/day (240 mg/m², about twice the recommended dose in humans on a mg/m² basis) caused reduced fetal weight.

**8.2 Lactation**

It is not known whether IRESSA is excreted in human milk. Animal studies indicate that gefitinib and its metabolites are present in rat milk at concentrations higher than those in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from IRESSA, advise women to discontinue breast-feeding during treatment with IRESSA.
### Data

Levels of gefitinib and its metabolites were 11-to-19-fold higher in milk than in blood, after oral exposure of lactating rats to a dose of 5 mg/kg.

### 8.3 Females and Males of Reproductive Potential

**Contraception**

Based on its mechanism of action and animal data, IRESSA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with IRESSA and for at least two weeks following completion of therapy.

**Infertility**

Treatment with IRESSA may result in reduced fertility in females of reproductive potential [see Nonclinical Toxicology (13.1)].

The two-week recommendation is based on approximately 6 half-lives for a non-genotoxic drug that can cause embryotoxicity. The elimination half-life of gefitinib is approximately 48 hours.

### 12.1 Mechanism of Action

The epidermal growth factor receptor (EGFR) is expressed on the cell surface of both normal and cancer cells and plays a role in the processes of cell growth and proliferation. Some EGFR activating mutations (exon 19 deletions or exon 21 point mutation L858R) within NSCLC cells have been identified as contributing to the promotion of tumor cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of in vivo expansion.

Inhibition of IGF- and PDGF-mediated signaling is based on data from the original IND (IND 54,576) review.
processes of metastasis.

Gefitinib reversibly inhibits the kinase activity of EGFR, preventing autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signalling and blocking EGFR-dependent proliferation. Gefitinib binding affinity for EGFR mutations is higher than its affinity for the wild type EGFR. Gefitinib reversibly inhibits the kinase activity of tyrosine EGFR. Gefitinib-mediated inhibition of EGFR prevents autophosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signalling and blocking EGFR-dependent proliferation. Gefitinib binding affinity for EGFR exon 19 deletion or exon 21 point mutation L858R mutations is higher than its affinity for the wild type EGFR. Gefitinib also inhibits IGF- and PDGF-mediated signaling at clinically relevant concentrations; inhibition of other tyrosine kinase receptors has not been fully characterized.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Gefitinib has been tested for genotoxicity in a series of in vitro (bacterial mutation, mouse lymphoma, and human lymphocyte) assays and an in vivo rat micronucleus test. Under the conditions of these assays, gefitinib did not cause genetic damage.

In a two-year carcinogenicity study in mice, administration of gefitinib at a dose of 270 mg/m²/day (approximately twice the recommended daily dose of 250 mg on a mg/m² basis; dose reduced from 375 mg/m²/day from week 22) caused hepatocellular adenomas in females. In a two-year carcinogenicity study in rats, administration of gefitinib at 60 mg/m²/day (approximately 0.4

The paragraph on fertility is based on findings from the previous review of Reproductive Toxicology of gefitinib under NDA 21399 and has been added here to support the infertility statement in Section 8.3.
recommended daily dose on a mg/m² basis) caused hepatocellular adenomas and hemangio
and hemagiosarcomas of the mesenteric lymph nodes in female rats. The clinical re
currence of these findings is unknown.

times of the recommended daily clinical dose on a mg/m² basis) caused hepatocellular adenomas and hemangio
and hemagiosarcomas of the mesenteric lymph nodes in female rats.

In a dedicated fertility study in rats at doses ≥ 120 mg/m² (approximately equal to the recommended human dose of gefitinib on a mg/m² basis), animals presented with an increased incidence of irregular estrous, decreased corpora lutea, and decreases in uterine implants and live embryos per litter.

3.3 Previous Reviews Referenced
IND 54,576, NDA 21,399

4 Pharmacology

4.1 Primary Pharmacology

The Applicant cited scientific literature evidence including data from Lynch et al (2004)¹ and Paez et al (2004)² identifying and characterizing sensitizing mutations in the intracellular kinase domain of epidermal growth factor receptor (EGFR) in tumor tissue samples obtained from a subset of patients with non-small cell lung cancer (NSCLC) who showed marked responses to ZD1839 (gefitinib). The most common of these mutations were a set of deletions within exon 19 (‘Ex19 del’) and a point mutation of exon 21 (‘L858R’). The exon 18 G719X mutation was also identified in these samples. The prevalence of EGFR mutations in NSCLC varies according to the different histological subtypes and patient ethnicity, being more common in adenocarcinoma than in squamous cell carcinoma, and more common in Asian patients (31 to 59%) than Caucasians (10 to 20%).

Lynch, et al (2004) quantified the activation of EGFR by measuring phosphorylation of the tyrosine¹⁰⁶⁸ residue, commonly used as a marker of EGFR autophosphorylation, in Cos-7 cells transiently transfected with wild-type or mutant (L747–P753insS deletion and the L858R missense ) EGFR constructs. Addition of EGF doubled or tripled the activation of both mutant EGFRs, compared to the activation of the wild-type receptor

and whereas the activation of wild-type EGFR was downregulated after 15 minutes (consistent with the internalization of the receptor), the two mutant receptors demonstrated continued activation for up to three hours (Figure 1; left panel). In cells pretreated with various concentrations of gefitinib, both mutant receptors were more sensitive than the wild-type receptor to inhibition of EGF-induced autophosphorylation of EGFR by gefitinib (Figure 1; right panel). Whereas the IC$_{50}$ for inhibition of the wild-type was 0.1µM, that for the mutants was 0.015 µM.

**Figure 1: Enhanced EGF–Dependent Activation of Mutant EGFR and Increased Sensitivity of Mutant EGFR to Inhibition by Gefitinib**

Consistent with the findings of Lynch, et al (2004), Paez, et al (2004) demonstrated that mutations in EGFR conferred in vitro sensitivity to gefitinib in four lung adenocarcinoma and bronchioloalveolar carcinoma cell lines. Treatment with 100 nM gefitinib completely inhibited EGFR autophosphorylation in H3255 cells (a cell line with the L858R mutation) as well as the phosphorylation of known downstream targets of EGFR such as the extracellular signal-regulated kinase 1/2 (ERK1/2) and the v-akt murine thymoma viral oncogene homolog (AKT kinase) (Figure 2). In this experiment, gefitinib was at least 50-fold more sensitive in inhibiting autophosphorylation in the mutant cell line than in wild-type cell lines.
Similarly, Tracy, et al (2004)\textsuperscript{3} investigated gefitinib-mediated growth inhibition in three bronchioloalveolar [NCI-H358, NCI-H1666 and NCI-H1781 (all \textit{EGFR}^{\text{WT}})] and six adenocarcinoma [NCI-A549, NCI-H23, NCI-H441, NCI-H2347, NCI-H3122 (all \textit{EGFR}^{\text{WT}}), and NCI-H3255 (\textit{EGFR}^{L858R})] cell lines. Gefitinib inhibited the growth of NCI-H1666 (IC\textsubscript{50}=2 \textmu M) and NCI-H3255 (IC\textsubscript{50}=0.04 \textmu M) cells, but was ineffective in inhibiting the growth of the remaining cell lines (IC\textsubscript{50} values >10 \textmu M). Both EGFR and AKT were shown to be constitutively phosphorylated in H3255, H1666, and H441 cell lines; in these cell lines, treatment with 1 \textmu M gefitinib \textit{completely} inhibited Akt phosphorylation only in the H3255 L858R mutant line (Figure 3). The investigators justified their use of 1 \textmu M gefitinib by stating that this is a concentration of gefitinib that can be achieved in serum in patients being treated with gefitinib and also one used by other investigators. The results of these studies are consistent with higher sensitivity of the H3255 (L858R mutant) cell line to gefitinib than cells expressing wild type EGFR.

Study Number: Pharmacology Report 01  
Title: Long Term Administration of Gefitinib in the NCI-H3255 NSCLC Xenograft Model

The Applicant used the NCI-H3255 L858R cell line in a xenograft model to assess the activity of a low dose of gefitinib.

Xenografts were established by subcutaneous implantation of $5 \times 10^6$ NCI-H3255 human NSCLC cells per mouse (in 200 µl of cell suspension including 50% matrigel), into the dorsal left flank of 6 week old female severe combined immune-deficient (SCID) mice. Mice were randomized into treatment groups when mean tumor volume reached approximately 0.4 cm$^3$. Mice were treated orally with either vehicle or gefitinib once daily beginning on Day 1 (the day after randomization). Tumor growth inhibition from the start of treatment was assessed by comparison of the change in geometric mean of the tumor volume for the control and treated groups using the Mousetrap application.

In the vehicle control group, tumors grew slowly over the treatment period of 75 days. Gefitinib treatment at a dose of 6.25 mg/kg orally once daily, caused significant tumor regression during the 75-day treatment period (Figure 4). By Day 18, gefitinib-mediated tumor growth inhibition was 251.2% and by Day 75 tumor growth inhibition was 156%. Daily administration of gefitinib had no remarkable effect on body weight compared to vehicle treated controls. Thus, gefitinib treatment resulted in significant tumor regression using the NCI-H3255 (L858R) EGFR mutant xenograft model.
Pharmacology Report 02: Long Term Administration of AZD9291 and Gefitinib in a PC9 NSCLC Xenograft Model

The Applicant assessed the activity of gefitinib against the human PC9 cell line (which contains the Ex19del activating EGFR mutation) in a mouse xenograft model. Xenografts were established in 6 week old female SCID mice by subcutaneous implantation of $5 \times 10^6$ cells per mouse, in 100 μl of cell suspension, including 50% matrigel, into the dorsal left flank. When mean tumor volume reached approximately 0.4 cm$^3$, mice were treated orally with either vehicle or gefitinib once daily from the day after randomization. Tumor growth inhibition was assessed by comparison of the mean change in tumor volume for the control and treated groups, using the Mousetrap application.

In the vehicle-treated control group, tumors showed exponential growth and mice had to be sacrificed due to tumor burden 17 to 21 days after the start of dosing. Daily doses of 6.25 and 25 mg/kg gefitinib resulted in tumor growth inhibition of 143% and 162%, respectively. At the dose of 6.25 mg/kg, gefitinib induced tumor regression and tumors were static by Day 21 but started to regrow by Day 49. At the higher dose of 25 mg/kg daily, gefitinib induced complete tumor regression and tumors were non-measurable by Day 42 and not visible by Day 105. Daily treatment with gefitinib did not have a significant effect on body weight.

Although the 25 mg/kg dose of gefitinib induced long lasting tumor regression in PC9 tumor-bearing SCID mice, the Applicant, stated that the 25 mg/kg (75 mg/m$^2$) dose is not clinically achievable due to wild-type toxicity.
In NDA 206995, AstraZeneca has submitted pharmacology data to support the activity of gefitinib in inhibition of signaling through several EGFR mutant proteins that are commonly found in patients with metastatic non-small cell lung cancer. I concur with Dr. Khasar’s conclusion that the current data in combination with the studies previously reviewed under NDA 21399 are sufficient, from a pharmacology/toxicology perspective, to support the approval of gefitinib for the treatment of patients with metastatic non-small lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R substitution mutations as detected by an FDA-approved test.