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Joan Claybrook, President

April 28, 2005

Lester Crawford, DVM, Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

RE: Supplement to Petition to the FDA to withdraw the lung cancer drug
gefitinib (Iressa)

Dear Commissioner Crawford:

Public Citizen, a nationwide consumer organization with a membership of more than 150,000 people, wishes to supplement its March 4, 2005 petition¹ (Docket number 2005P-0094), which called for the immediate removal from the market of the drug Iressa (gefitinib; AstraZeneca) due to its proven failure to reduce mortality among patients who are getting the drug as second and third line therapy, its failure to improve patients' quality of life, and its potential to cause serious adverse events including fatal interstitial pneumonia. A newly available government-sponsored clinical trial brings to four the number of studies in which Iressa has failed to reduce mortality.

Iressa was approved under an accelerated approval process (Subpart H), which allows approval based on the surrogate endpoint of tumor shrinkage. However, in an uncontrolled trial, shrinkage occurred in only 10% of patients with non-small cell lung cancer (NSCLC) who had failed two other chemotherapy regimens. As part of Subpart H, sponsors are required to conduct long-term mortality studies.

On May 1, 2003, Public Citizen asked that Iressa not be approved² because, in addition to the minimal 10% response rate, two large Phase III trials (INTACT 1 and 2) with Iressa as first-line therapy (no treatment prior to

¹ <http://www.citizen.org/publications/release.cfm?ID=7369>

² <http://www.citizen.org/publications/release.cfm?ID=7242>

2005P-0094

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Iressa) completed before drug approval were clearly negative with respect to survival.

On December 17, 2004, FDA announced the failure of a third large (1,690 patients), randomized, controlled trial (ISEL), that had been required as a condition of approval.³ Based on this failure, on March 4, 2005, Public Citizen petitioned for FDA to withdraw Iressa from the market.⁴ Under the accelerated approval process, this demonstrated lack of efficacy could have triggered the withdrawal of the drug.

As a consequence of these failures to prolong the lives of NSCLC patients, AstraZeneca withdrew its European Marketing Authorization Application for Iressa on January 4, 2005.

On April 19, 2005, the National Institutes of Health (NIH) announced the failure of still another large clinical trial. Iressa treatment failed to improve either overall survival or progression-free survival in 672 NSCLC patients with Stage III cancer who had previously completed a combined chemotherapy and radiation regimen.⁵ As a result, the trial was halted after an interim data analysis.

In how many trials does Iressa have to fail before it is withdrawn from the market and returned to an Investigational New Drug (IND) status? Under an IND, studies to attempt to determine the characteristics of patients who might benefit could continue. As long as Iressa has full approval status, patients risk being diverted from the currently approved drug, Tarceva, that does provide a survival benefit, as AstraZeneca itself acknowledged in its "Dear Doctor" letter.⁶

The effort by AstraZeneca to use post-hoc subanalyses to find subsets of patients that benefit from Iressa is not statistically valid. As FDA's Dr. Robert Temple commented: "The study, after all, failed. You had opportunities to identify subsets before the study that would be your primary analysis, but you didn't think that they were good enough to do that. . . . [T]hese are after-the-fact subset analyses in a study that did not win. That is different from subset analyses in a study that did win."⁷

It is unconscionable to keep Iressa on the market, dosing patients for whom it offers no benefit while exposing them to the risk of serious adverse events. With 331 new Iressa prescriptions per week (as of mid-February), it is clear that a large number of patients continue to be given a drug with no proven benefit but many risks.

³ <http://www.fda.gov/bbs/topics/news/2004/new01145.html>

⁴ <http://www.citizen.org/publications/release.cfm?ID=7369>

⁵ <http://www.cancer.gov/newscenter/pressreleases/gefitinibNSCLC/print?page=&keyword=>

⁶ <http://www.iressa-us.com/dr.pdf>

⁷ <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4095T2.htm>

With four negative mortality studies, the failure to remove Iressa from the market will mean that Subpart H has effectively become a back door to FDA approval, with a concomitant lowering of FDA approval standards. To restore its credibility, FDA should promptly withdraw Iressa from the market.

Yours sincerely,

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