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Recd
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The Food & Drugs Administration,
US Department of Health & Human Services
Food & Drug Administration
Centre for Drug Evaluation & Research
5600, Fishers lane
Rockville, MD 20857

RECEIVED

JUN 25 2007

CDER White Oak DR 1

Dear Sir / Madam,

This is with reference to 'Draft guidance for industry: Bio-Equivalence recommendations for specific products (issued May 2007)' cited at your website 'www.fda.gov/cder/guidance/bioequivalence/default.htm' and seeking public comment/opinion.

We wish to point out a factual error published in the above site for **Erlotinib Hydrochloride**. The drug substance/product **Erlotinib Hydrochloride** is not cytotoxic as mentioned and hence the recommendations for bio-equivalence need revision. The information quoted from the originator/innovator company's package insert and also from other leading sources is provided below:

Originator's package insert:

- The package insert for **Erlotinib Hydrochloride** ('Tarceva' of Genentech-OSI oncology) has not indicated any 'cytotoxicity' warning for this drug.
- The above package insert specifically mentions on page-24 that the drug 'did not cause any genetic damage.... and did not impair fertility in the male or female rats' (<http://www.fda.gov/cder/foi/label/2007/021743s007lbl.pdf>)

BC Cancer agency - Cancer drug manual:

- The drug manual information furnished for the drug 'Erlotinib' by the 'BC Cancer agency drug manual' did not classify this drug as 'cytotoxic' (page-1)
- Administration of the drug as a suspension in water has been recommended (page-4) for patients with feeding tubes. This aspect clearly suggests the non-cytotoxic nature of the drug.

(http://www.bccancer.bc.ca/NR/rdoniyres/880586AD-1B2F-4912-BFE6-BD3728F67918/19527/erlotinibmonograph_2Nov06.pdf)

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Cigna health care coverage position:

- ≡ The following information is provided by 'Cigna healthcare coverage position' (No.: 5010, Page-2)
- ≡ 'Erlotinib showed, no clinical benefit in combination with cytotoxic chemotherapeutic agents in first line therapy.
- ≡ 'Erlotinib' has a more acceptable toxicity profile compared to cytotoxic chemotherapeutic agents currently used

This information also clearly demarcates the classification for 'Erlotinib' as non-cytotoxic

(http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/pharmacy/ph_5010_coveragepositioncriteria_tarceva.pdf)

Scientific discussion – EMEA review (European Medicinal Evaluation Agency)

The comprehensive scientific discussion and review on erlotinib hydrochloride by EMEA also do not indicate any cytotoxicity for the drug. It is mentioned as non-teratogenic and reported to be negative in genotoxicity tests. (Pages-10, 11)

The commercial manufacturing process is reported to involve 'standard technology with standard equipment' indicating that no special containment facility is employed as is essentially needed for manufacture of 'cytotoxic' drug substances. (Pages-3)

(<http://www.emea.europa.eu/humandocs/PDFs/EPAR/tarceva/061805en6.pdf>)

In view of the information cited above, we request you to revise the information for 'Erlotinib Hydrochloride' furnished in your site.

We also wish to mention that a Para-IV certification of the drug is due in November 2008 and your clarification in this respect will help us to manufacture the generic version of the drug making it available to many needy patients across the globe.

Past clarifications:

FDA has clarified to us in the past that anti-cancer/oncological drugs like Letrozole, Anastrozole, Bicalutamide, Imatinib mesylate etc. are non cytotoxic taking into consideration the innovator's labeling instructions and other data.

Conclusion:

We request you to review the references furnished and provide us clarification and guidance with respect to the classification (non-cytotoxic nature) and Bio-Equivalence requirements

Dr AKS Bhujanga Rao
President-(R&D & Tech)

Contains Nonbinding Recommendations

Draft Guidance on Erlotinib Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Erlotinib Hydrochloride

Form/Route: Tablets/Oral

Recommended studies: 1 study

Type of study: Fasting

Design: Multiple-dose, steady-state, two-way crossover *in vivo*

Strength: 150 mg

Subjects: Non-small cell lung cancer patients for whom erlotinib is indicated. Females should not be pregnant, and if applicable, should practice abstinence or contraception during and for at least two weeks following the study. Females should be advised against breast-feeding while receiving the drug.

Additional Comments:

Dosing on each treatment should continue for a sufficient time to allow equilibration on the test and reference treatments, hence for four to five half-lives prior to bioequivalence study plasma sampling. Similarly, sufficient time for re-equilibration should be allowed for the crossover treatment. Washout between treatment periods is not recommended. The study should be conducted in all patients using the same dosage strength tablet.

→ Submission of an Investigational New Drug Application (IND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as Erlotinib (See 21 C.F.R § 320.31).

Analytes to measure (in appropriate biological fluid): Erlotinib in plasma

Bioequivalence based on (90% CI): Erlotinib

Waiver request of in-vivo testing: 100 mg and 25 mg based on (i) acceptable bioequivalence studies on the 150 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.fda.gov/cder/ogd/index.htm>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.