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Bioequivalence of a New Generic Formulation of Erlotinib Hydrochloride 150 mg Tablets versus Tarceva in Healthy Volunteers under Fasting Conditions

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Abstract

Erlotinib is a potent and highly selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase used in the treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) and was recently approved for use in combination with gemcitabine.

A single center, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, crossover design bioequivalence study was conducted in 36 fasting, healthy volunteers to compare pharmacokinetics profile of a new Erlotinib generic formulation (Erlotinib tablets 150 mg, Hikma Pharmaceuticals) with those of the reference product(Tarceva, OSI Pharmaceuticals, USA). The study was performed by CRO PHARMA MEDICA RESEARCH INC. (Canada) in accordance with Good Clinical Practices and the applicable regulatory requirements.

One tablet of each formulation was administered with water after a 10 hour overnight fast. In each study period, twenty (20) blood samples were collected by venipuncture in pre-cooled Vacutainers containing EDTA. The first blood sample (2×6 mL) was collected prior to drug administration while the others (1×6 mL each) were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 14, 24, 36, 48 and 72 hours after drug administration. The drug administrations were separated by a washout period of 14 calendar days.

Plasma samples were analyzed for Erlotinib by a validated LC/MS/MS method. For a 150 mg dose of erlotinib, the analytical range was approximately 1ng/mL to 3000 ng/mL. Descriptive statistics were used to summarize adverse events, safety results and demographic variables (age, height, weight and BMI)

The main pharmacokinetic parameters of interest for this study were C_{max}, AUC_{0-T} and $AUC_{0-\infty}$. Other parameters such as T_{max}, $AUC_{T/\infty}$, K_{el} and $T_{1/2el}$ were provided for information purposes only. The natural logarithmic transformation of C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ was used for all statistical inference. The mean (CV %) of C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ for Erlotinib were 1108.89 ng/ml (28%), 23764.87 ng.h/ml (31%) and 25489.41 ng.h/ml (36%) versus 1073.06 ng/ml (35%), 24607.87ng.h/ml (33%) and 26565.89ng.h/ml (40%) for Tarceva. The 90% confidence intervals of C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ for Erlotinib 150 mg were (96.08%-121.54%), (91.34 %-103.42%) and (89.99 %-103.22%) respectively. The ratio of the geometric LS means for the test to reference C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ for Erlotinib 150 mg were 108 %, 97% and 96% respectively.

The analysis of variance (ANOVA) did not show any significant difference between the two formulations and 90% confidence intervals (CI) fell within the acceptable range for bioequivalence. Based on these statistical inferences it was concluded that the two formulations of Erlotinib exhibited comparable pharmacokinetics profiles.

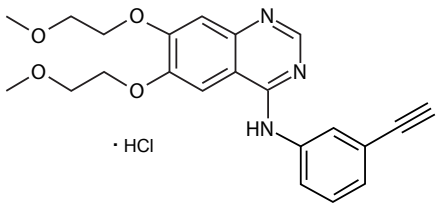
Keywords: Generic formulation; Pharmacokinetic parameters; Inhibitor; Erlotinib hydrochloride

Introduction

Erlotinib is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine [1]. Erlotinib is available in the market as the hydrochloride salt [1]. It is manufactured by OSI pharmaceuticals, Inc. and Genentech in the USA and by Roche in the EU under the trade name of Tarceva [2]. Tarceva is available in the market in three dosage strengths containing Erlotinib hydrochloride (27.3, 109.3 and 163.9 mg) equivalent to 25, 100 and 150 mg of Erlotinib [1].

Erlotinib Hydrochloride has the following molecular formula: $C_{22}H_{23}N_3O_4$.HCl and a molecular weight of 429.90. Erlotinib Hydrochloride is very slightly soluble in water. Aqueous solubility is dependent on pH with increased solubility at a pH less than 5 due to the protonation of the secondary amine [1].

Erlotinib has the following structural formula:



Erlotiniob. HCl is a class 2 compound according to the

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Biopharmaceutics Classification Systems (BCS) which is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug development tool that allows estimation of the contributions of the drug where solubility, permeability and the drug formulation dissolution profile, all of which collectively affect oral absorption of drugs. BCS class II and IV drugs which have low solubility provide a number of challenges for formulation scientists working on oral delivery of drugs. For example, a BCS Class II compound is permeable but relatively insoluble, is likely not a good clinical candidate without the use of enhanced formulation techniques aimed at increasing solubility or rate of dissolution [3].

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen and was recently approved for use in combination with gemcitabine chemotherapy for treatment of locally advanced, inoperable, or metastatic pancreatic cancer [4].

Lung cancer is the leading cause of cancer death in North America and worldwide. Non-small-cell lung cancer (NSCLC) is a heterogenous aggregate of histologies, including squamous cell carcinoma, adenocarcinoma and large cell carcinoma, and represents approximately 80-85 % of all lung cancers [2].

Erlotinib is a potent and highly selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase [5]. At nanomolar concentrations, erlotinib inhibits EGFR-dependent proliferation of tumor cells in vitro and blocks cell-cycle progression in the G1 phase. EGFR is highly expressed in a wide spectrum of tumors, such as head and neck, breast, brain, lung, cervical, bladder, gastrointestinal, and renal tumors, as well as other epithelial malignancies, and is a rational strategic target for anticancer therapy [4].

Following oral administration, Erlotinib is rapidly absorbed from the gastrointestinal tract and peak plasma levels are reached 1.4 hours and about 3 hours post-dose in both healthy subjects and cancer patients [6]. Oral absolute bioavailability of erlotinib was shown to be (mean) 59% (95% CI 55-63) in healthy subjects [7] and (median) 76% (90% CI 53-111) in cancer patients [8]. Both Cmax and AUC24 values tended to be proportional to the erlotinib dose in the dose range of 25–200 mg/day. Comparing pharmacokinetic results from day 1 with those on day 24, there were no differences in paired intraindividual apparent total oral clearance (CL/F) across the dose range of 50–200mg, indicating dose-independent pharmacokinetics. Steady state was reached in 7-8 days [6].

Wide interindividual variability in erlotinib exposure (up to 7-fold) was seen in all pharmacokinetic studies, which remains mostly unexplained [8].

Solubility of erlotinib is pH dependent and decreases with increasing pH. Thus, absorption and bioavailability of erlotinib can alter by changes in gastric/ intestinal pH due to disease and concomitant medication. This was confirmed in drug-drug interaction studies with the proton pump inhibitor omeprazole and the histamine H2-receptor antagonist ranitidine, as both drugs modulate gastric pH [1].

Erlotinib in clinical studies was administered as 6*25 mg and 1*150 mg oral tablets in a single-dose study in healthy subjects and bioequivalence between two tablet formulations was shown; the geometric mean ratios for AUC_{∞} and Cmax of Erlotinib were 1.0 and 0.95, respectively, with 90% CIs within the predefined range of 0.80–1.25 [7]. Elimination half life for Erlotinib was 16±7 hr (For 6*25 mg dose) and 17 ± 8 hr (For 1*150 mg dose).

Bioavailability of Erlotinib increases with concomitant food intake. In a single-dose study in 18 healthy subjects with administration of erlotinib 150 mg, AUC_{∞} values approximately Doubled under fed conditions; however, high variability in the ranges of pharmacokinetic parameters because of food intake was observed.

Following absorption, Erlotinib is highly bound (92-95%) to plasma proteins (Albumin and α-1 acid glycoprotein (AAG) [1].

Erlotinib is extensively metabolized predominantly by CYP3A4 and, to a lesser extent, by CYP1A2, and the extrahepatic isoform CYP1A1 with metabolites excreted by the biliary system. A number of metabolites of erlotinib were identified in rats and dogs, with O-demethylation, oxidation of the acetylene moiety, and aromatic hydroxylation as the major biotransformation pathways [9]. In a study in four healthy male subjects receiving 100 mg ^{14}C-erlotinib, 83 ± 6.8% of total radioactivity was recovered in faeces, with >90% as metabolites indicating that metabolism is the main mode of erlotinib elimination. Most metabolites of erlotinib are due to O-demethylation of the side chains and formation of O-desmethyl-erlotinib (M14, OSI-420) followed by oxidation to a carboxylic acid (M11), while the other major pathways are based on oxidation of the acetylene moiety to a carboxylic acid (M6) and hydroxylation of the aromatic ring (M16). In total, 14 metabolites could be identified in human plasma [6]. Among 14 metabolites of erlotinib identified to date, only OSI-420 was shown to have pharmacological activity (10). OSI-420 plasma concentrations were found to be about 7-10% of those of parent compound [11]. Since no data on the pharmacokinetics of erlotinib in tumour tissue are available it is unclear whether the metabolite may contribute to the antitumour activity of Erlotinib [6].

Cotreatment with the potent CYP3A4 inhibitor Ketoconazole increased erlotinib AUC by two thirds. Pre or Cotreatment with CYP3A4 inducers, such as rifampicin, or antiepiletics (Phenytoin, carbamazepine and barbiturates) increased erlotinib clearance by threefold and reduced AUC by two thirds [12].

The aim of this study was to compare the bioavailability of two formulations of Erlotinib Hydrochloride 150 mg tablets. A generic formulation developed at Hikma Pharmaceuticals PLC and a reference one (Tarceva, OSI Pharmaceuticals, Melville, NY; Roche, Basel, Switzerland; Genentech, South san Francisco,CA.USA), after a single oral administration of 150 mg tablet to healthy volunteers.

Materials and Methods

Ethics

This study was only commenced after a written approval obtained by the Ethics Review Board (ERB), Optimum Clinical Research Inc.

This research was carried out in accordance with current FDA guidance documents [12], Current EMEA guidance documents [13], Good Clinical Practice (GCP) as set out by the International Conference on Harmonization (ICH) and the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312) and the World Medical Association Declaration of Helsinki (Seoul, October 2008). The Clinical Trial Application for the study was reviewed by Health Canada and the study drug was not administered until the 'No Objection Letter (NOL)' has been received.

Volunteers were informed about the study procedure and signed

the informed consent form. The code that was assigned to the protocol of the study was 2013-3268. Hikma Pharmaceuticals ensured that the investigational product was manufactured in accordance with GMP; the labeling also complied with the international regulatory requirements.

Drugs

The reference product was Tarceva tablets 150 mg (containing 150 mg Erlotinib as Erlotinib Hydrochloride) manufactured by OSI Pharmaceuticals, USA (batch number: 1088301 CW, expiry date: 07/2015). The test product was Erlotinib tablets 150 mg as Erlotinib hydrochloride (Batch Number 2130703) developed by Hikma Pharmaceuticals PLC, manufactured 07/2013.

Subjects

Thirty-eight (38) subjects were enrolled in the study and thirty-six (36) completed the study. The study population consisted of healthy, non-smoking, male and female volunteers of non-childbearing potential.

Data from the literature indicates a coefficient of variation (CV) for Erlotinib Cmax of up to 20%. Assuming a 20% intra-subject variability and a difference between the treatment means of 7.5% or less, the necessary sample size for a 90% probability of the 90% confidence interval of the treatment means ratio to be within the 80.00–125.00% range was estimated to be 34 subjects.

Four (4) extra subjects were included into the study to account for potential dropouts. Therefore, 38 subjects were enrolled into this study.

Since Erlotinib is considered a Pregnancy Risk Category D drug as defined by the FDA, only male subjects and female subjects of non-childbearing potential were enrolled in this study.

Also, all volunteers were healthy non-smoking, 18 years of age or older with a body mass index (BMI) greater than or equal to 19 and below 30 kg/m^2.

All subjects were selected according to the inclusion and exclusion criteria. They were healthy according to medical history, physical examination (including vital signs) and laboratory tests (hematology, biochemistry, and urinalysis). Also, all volunteers were negative regarding HIV, Hepatitis B and Hepatitis C tests as well as negative screening of ethyl alcohol and drugs of abuse in urine.

Enrolling healthy subjects in this study is complying with the current FDA bioequivalence recommendation [11], as well as Current EMEA guidance documents [12].

Study design and blood sampling

This study was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, comparative bioavailability study. Subjects were randomly assigned to one treatment sequence according to a predetermined computer-generated randomization scheme (procedure PLAN in SAS®). Subjects were assigned consecutive subject numbers in an ascending order. Each number identified a subject and determined the sequence of drug product administration according to the randomization scheme.

Subjects were confined in the clinical facility from 10 hours prior to drug administration until at least 24 hours post-dose.

In each study period, a single 150 mg dose of erlotinib tablets was orally administered with about 240 mL of water. The volunteers were asked to fast overnight for 10 h. Subjects remained seated for at least the first 4 hours following each drug administration. In each study period, twenty blood samples were collected by venipuncture in pre-cooled Vacutainers containing K_2EDTA. The first blood sample (2 x 6 mL) was collected prior to drug administration while the others (1×6 mL each) were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 14, 24, 36, 48 and 72 hours after drug administration.

The drug administrations were separated by 14 calendar days. Urine drug and ethyl alcohol screening was performed before each period of the study. Hematology and biochemistry tests were repeated after the collection of the last blood sample of the study. Safety was evaluated through the assessment of adverse events, and laboratory tests. All adverse events that occurred during the study were documented. Subjects were questioned about any symptoms or unexpected occurrences during the study. All adverse events, regardless of severity or relationship to the study drug, were recorded in the case report forms.

Drug assay

Plasma concentrations of Erlotinib in subject samples were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) achiral method developed and validated at the Bioanalytical Laboratory of Pharma Medica Research Inc. The analytical method procedures comply with the FDA guidance for industry: Bioanalytical method validation (May 2001).

The method involved protein precipitation. The standard calibration range was from 1.00 to 3000 ng/mL using a plasma sample volume of 0.200 mL. Plasma samples were precipitated with a precipitation solvent and 0.100 mL of the supernatant was transferred into polypropylene vials for LC-MS/MS analysis. Sample analysis was conducted using reversed phase chromatography. Erlotinib was analyzed in the mass spectrometer SCIEX API 4000 using positive scan mode with a parent-daughter transition of 394-336 amu. Similarly, the internal standard was analyzed using a parent-daughter transition of 400-339 amu. The expected retention time for Erlotinib and the internal standard is approximately 1.2 minutes. Although the retention time of both Erlotinib and the internal standard is the same, the MS/MS technique allows distinguishing between the two molecules for quantitation, because they have different parent-daughter transitions.

Pharmacokinetic parameters and statistical analysis

A noncompartmental model was used to determine the pharmacokinetic parameters of Erlotinib. The main pharmacokinetic parameters of interest for this study were C_{max}, AUC_{0-T} and $AUC_{0-\infty}$. Other parameters such as T_{max}, K_{el} and $T_{1/2el}$ were provided for information purposes only. Pharmacokinetic parameters were estimated for Erlotinib using a noncompartmental approach in SAS® (Statistical Analysis System). The natural logarithmic transformation of C_{max}, AUC_{0-T} and $AUC_{0-\infty}$ was used for all statistical inference.

Statistical analysis was performed on quality assured data from subjects in the statistical dataset. The PROC GLM procedure from SAS® was used. The GLM procedure uses the method of least squares to fit general linear models. PROC GLM handles models relating one or several continuous dependent variables to one or several independent variables. The independent variables can be either classification variables, which divide the observations into discrete groups, or continuous variables. Thus, the GLM procedure can be used for many different analyses.

Analysis of variance (ANOVA) was performed on log-transformed AUC_t, AUC_{inf} and C_{max} and on untransformed T_{max}, K_{el} and T_{half}

parameters. The significance of the sequence, period, treatment and subject-within-sequence effects was tested.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf} and C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

Results

The bioequivalence study was conducted in 38 healthy volunteers. Demographic characteristics (mean [SD]) for the overall group included in the study was as follows (Mean ± SD): age, 40 (± 11) years; weight 76 (± 12.3) kg; height, 171.7 (± 8.5) cm; and BMI, 25.7 (± 3.0) kg/m^2 (Table 1).

Under fasting conditions, C_{max}, T_{max}, AUC_{0-T} and $AUC_{0-\infty}$ for Erlotinib tablets 150 mg and Tarceva were similar in healthy adult volunteers. The mean plasma concentrations versus time (pharmacokinetic) profiles were superimposed on each other (Figure 1). The mean parameters tested C_{max}, T_{max}, AUC_{0-T} and $AUC_{0-\infty}$ were similar for both formulations (Tables 2 and 3).

Thirty-eight (38) subjects were enrolled in the study and 36 subjects completed the study. Two of the volunteers were withdrawn from the study in period one due to noncompliance (dismissed doses). There was no significant deviation or adverse event that could affect the pharmacokinetic profile.

Thirteen (13) of the thirty-six subjects included in the study experienced a total of fifteen (15) adverse events during the study. Six (6) adverse events (5 different types) were reported after the single dose administration of the test product and nine (9) adverse events (7 different types) were reported after the single dose administration of the reference product. All adverse events were judged to be mild in severity. Hypertension is the most frequent adverse event in the study (total of 5 cases were observed- 3 with the reference product administration and 2 with the test product administration).

		Statistical and Pharmacokinetic Dataset N = 36	Safety Dataset N = 38
Age (years)	**Mean ± SD** **Median** **Range**	40 ± 11 40.5 23 - 59	39 ± 11 40.5 23 - 59
Age Group	**<18** **18 - 40** **41 - 64** **65 – 75** **>75**	0 (0.0%) 18 (50.0%) 18 (50.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 19 (50.0%) 19 (50.0%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	31 (86.1%) 5 (13.9%)	33 (86.8%) 5 (13.2%)
Race	**Asian** **Black** **White** **Other**	6 (16.7%) 10 (27.8%) 20 (55.6%) 0 (0.0%)	6 (15.8%) 11 (28.9%) 21 (55.3%) 0 (0.0%)
Ethnicity	**Hispanic/Latino**	10 (27.8%)	10 (26.3%)
BMI (kg/m^2)	**Mean ± SD Median Range**	25.7 ± 3.0 26.0 21.0 - 30.0	25.7 ± 3.1 26.0 20.7 - 30.0
Height (cm)	**Mean ± SD Median Range**	171.7 ± 8.5 171.3 155.2 - 190.0	172.3 ± 9.0 171.6 155.2 - 193.3
Weight (kg)	**Mean ± SD Median Range**	76.0 ± 12.3 75.3 50.5 - 101.6	76.3 ± 12.1 76.0 50.5 - 101.6

Table 1: Demographic characteristics (mean [SD]) for the overall group included in the study.

Parameter	Test		Reference	
	Mean	CV%	Mean	CV%
C_{max} (ng/mL)	1108.89	28	1073.06	35
T_{max} (hours)	2.22	37.99	3.48	162.49
AUC_{0-T} (ng·h/mL)	23764.87	31	24607.87	33
$AUC_{0-\infty}$ (ng·h/mL)	25489.41	36	26565.89	40
$AUC_{T/\infty}$ (%)	94.64	5.49	93.95	7.28
K_{el} (hours^{-1})	0.0603	56.74	0.0597	52.44
$T_{½el}$ (hours)	14.33	43.87	14.67	48.08

Table 2: The Pharmacokinetic Parameters of Erlotinib tablets 150 mg versus Tarceva.

Parameter	Intra-Subject C.V. (%)	Geometric LSMEANS		Ratio (%)	90% Confidence Limits	
		Test	Reference		Lower	Upper
C_{max} (ng/mL)	30	1064.91	985.43	108.07	96.08	121.54
AUC_{0-T} (ng·h/mL)	16	22571.77	23224.21	97.19	91.34	103.42
$AUC_{0-\infty}$ (ng·h/mL)	17	23892.17	24789.67	96.38	89.99	103.22

Table 3: Comparison of results with standards for Bioequivalence.

Discussion

Two drug products (of the same active ingredient) are therapeutically equivalent when the rate and extent of biologic absorption of the active ingredients is essentially similar. Area under the curve (AUC) is accepted as a good indicator of extent of absorption, whereas Cmax and Tmax are considered estimators of the rate of absorption. Two internationally recognized organizations (U.S. Food and Drug Administration and European Agency for the Evaluation of Medicinal Products) have proposed that bioequivalence can only be assumed when the characteristic parameters of bioavailability show no more than a defined difference, which depends on the nature of the drug, the subject population, and the clinical end point.

The ratios of LSM and 90% confidence intervals for the pharmacokinetic parameters (C_{max}, AUC_{0-T} and $AUC_{0-\infty}$) of Erlotinib tablets 150 mg versus Tarceva tablets 150 mg under fasting conditions were within 80% to 125% FDA acceptance range for generic drugs which indicated that Erlotinib tablets 150 mg and Tarceva tablets 150 mg are bioequivalent under fasting conditions. The pharmacokinetics of the formulations tested was the same and healthy subjects were well tolerated to Erlotinib and no major side effects were observed.

Conclusion

Based on statistical results, it can be concluded that both products tested in this study satisfy with regulatory requirements to be claimed bioequivalent. According to the above, the test product can be considered interchangeable with the reference based on their biopharmaceutical performance. Both products of erlotinib included in this study were well tolerated, bioequivalent, and both products can be considered equally effective and interchangeable in medical practice based on the pharmacokinetic effect.

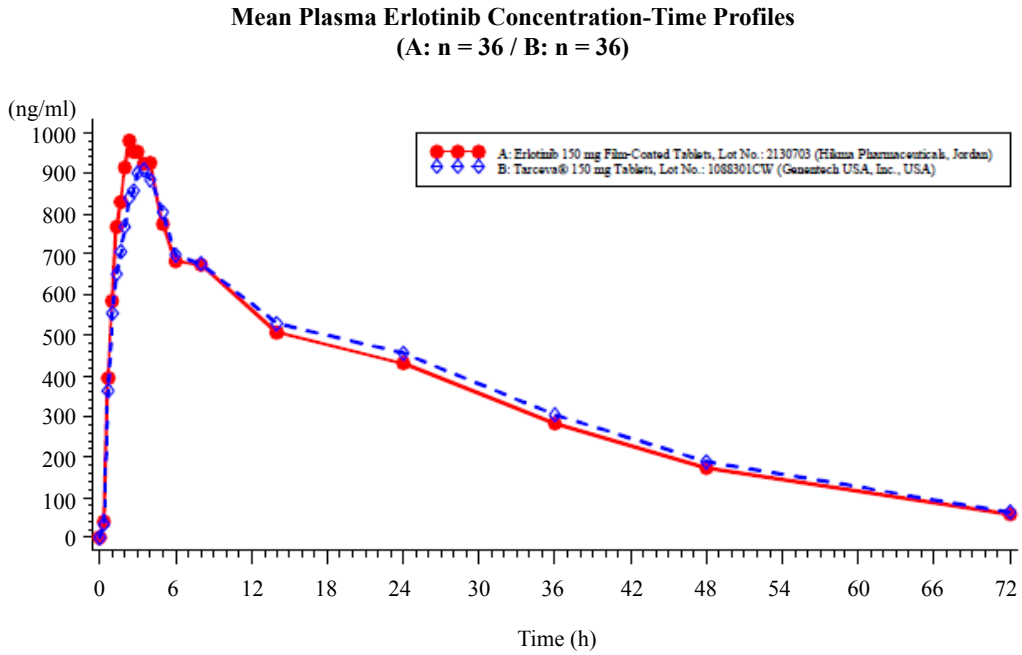

Figure 1: Plasma concentrations of Erlotinib tablets 150 mg (Test) and Tarceva (Reference).

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