European Medicines Agency
Evaluation of Medicines for Human Use

Doc Ref:EMA/231873/2010
London 29 April 2010

CHMP ASSESSMENT REPORT

FOR

Raloxifene Teva

International Nonproprietary Name: raloxifene
Procedure No. EMEA/H/C/001075

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

Teva Pharma B.V. submitted on 02 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Raloxifene Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: Evista 60 mg Film-coated Tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 05 August 1998
- Marketing authorisation granted by:
  - Community
- Marketing authorisation number: EU/1/98/073/001-004

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Evista 60 mg Film-coated Tablet
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 05 August 1998
- Marketing authorisation granted by:
  - Community
- Marketing authorisation number: EU/1/98/073/001-004
- Bioavailability study number(s): 2008-1686, 2008-1729, 2009-2140.

The Rapporteur appointed by the CHMP was Robert Hemmings.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

On 22 August 2008 the transfer of the marketing authorisation from Eli Lilly Nederland B.V. to Daiichi Sankyo Europe GmbH was accepted and the respective Commission Decision was issued.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 02 October 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 January 2009.
- During the meeting on 16-19 February 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 February 2009.
- A clarification meeting requested by the Applicant took place on 26 March 2009 with the Rapporteur, the Agency and the Applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 November 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 December 2009.
- During the CHMP meeting on 18-21 January, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding issues on 27 January 2010.
- During the meeting on 15-18 February 2010 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Raloxifene Teva on 18 February 2010.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Raloxifene Teva 60 mg Film-coated Tablets is a generic medicinal product containing raloxifene hydrochloride as active substance. The reference medicinal product Evista 60 mg Film-coated Tablets has been authorised for at least 10 years in the Community (Eli Lilly Nederland B.V., registered since 05 August 1998). The active substance of the reference product is raloxifene hydrochloride.

Studies have demonstrated the satisfactory quality of Raloxifene Teva, and its bioequivalence with the reference product Evista.

Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated. When determining the choice of raloxifene or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits.

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fractures. As a selective oestrogen receptor modulator (SERM), raloxifene has selective agonist or antagonist activities on tissues responsive to oestrogen. It acts as an agonist on bone and partially on cholesterol metabolism (decrease in total and LDL-cholesterol), but not in the hypothalamus or in the uterine or breast tissues.
Raloxifene biological actions, like those of oestrogen, are mediated through high affinity binding to oestrogen receptors and regulation of gene expression. This binding results in differential expression of multiple oestrogen-regulated genes in different tissues. Recent data suggests that the oestrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

The recommended dose is one tablet daily by oral administration, which may be taken at any time of the day without regard to meals. No dose adjustment is necessary for the elderly. Due to the nature of this disease process, raloxifene is intended for long term use.
Generally calcium and vitamin D supplements are advised in women with a low dietary intake.
Use in renal impairment: raloxifene should not be used in patients with severe renal impairment. In patients with moderate and mild renal impairment, raloxifene should be used with caution.
Use in hepatic impairment: raloxifene should not be used in patients with hepatic impairment.

Raloxifene is associated with an increased risk for venous thromboembolic events that is similar to the reported risk associated with current use of hormone replacement therapy. The risk-benefit balance should be considered in patients at risk of venous thromboembolic events of any aetiology. Raloxifene should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible in case of the illness, or from 3 days before the immobilisation occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile.

2.2 Quality aspects

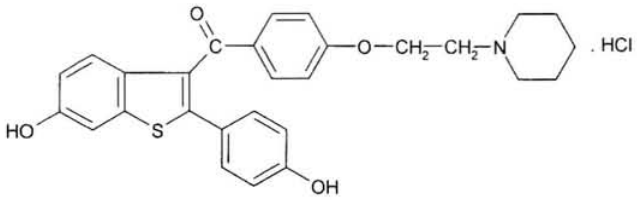
Introduction

The product is presented as film-coated tablets for oral use containing 60 mg of raloxifene hydrochloride as active substance
Other ingredients are defined in the SPC section 6.1.

The tablets are packed in transparent PVC/PVdC - Aluminium blisters.

Active Substance

Raloxifene hydrochloride is the common name for the chemical substance [6-Hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl]-[4-[2-(1- piperidinyl)ethoxy]phenyl]methanone hydrochloride. The molecular formula is $C_{28}H_{27}NO_4S.HCl$, with the relative molecular mass 510.05 and the following structural formula:



The active substance is well known and has been satisfactorily characterised. It forms a pale yellow powder practically insoluble in water and methanol, freely soluble in *N*,*N*-dimethylformamide. Characterisation data provided confirms that there are five potential polymorphs for this drug substance. The applicant satisfactorily supported the non-conversion of the polymorphic form obtained after synthesis.

Manufacture
Raloxifene hydrochloride is supplied by one manufacturer only. An Active Substance Master File was submitted to support the quality of active substance. A detailed description of the manufacturing process, including process flow diagram and in-process controls were provided and there is evidence that the process is under control and delivers an active substance of consistent quality.

Specification
The drug substance specification as tested by the finished product manufacturer includes relevant tests with justified limits with regards to description, identification, heavy metals, sulphated ash, loss on drying, assay, related substances, residual solvents, density and particle size distribution.
Adequate validation data was presented for the in-house analytical methods. Satisfactory batch analysis results were provided for three batches.

Stability
ICH compliant stability studies in accelerated (40 ± 2 °C/75 ± 5 % RH) and long-term storage conditions (25 ± 2 °C/60 ± 5 % RH) have been performed up to 6 months and 72 months, respectively. The following parameters were investigated: appearance, water content, related substances, and assay. The stability data support the proposed re-test period of 24 months with no special storage conditions.

Finished Product

Pharmaceutical Development
The aim was to obtain an immediate-release tablet containing qualitatively and quantitatively the same drug substance and exhibiting the same bioavailability as the reference product Evista 60 mg Film-coated Tablets, marketed by Eli Lilly.
All excipients used in the proposed generic product are standard and a satisfactory justification for the choice of the excipients is provided.
The impurity profiles of the generic product and the reference product were presented and found to be similar.

Several trial batches were manufactured using different manufacturing processes and different formulations in order to select adequate excipients and manufacturing conditions to develop tablets that exhibit acceptable physical and chemical characteristics.
Satisfactory data are provided to justify the proposed manufacturing process of the finished product.
The product is packed in transparent PVC/PVdC – aluminium blisters inside a cardboard box.

Adventitious Agents
The active substance, raloxifene hydrochloride, and all excipients are absent of BSE/TSE risk.

Manufacture of the Product
A detailed description of the manufacturing process and in-process controls was provided. The manufacturing process is a standard process utilised in tablet manufacture
Process validation data were provided and the critical steps of the manufacturing process have been identified and validated.

Product Specification
The finished product specifications include the following parameters: description, appearance, identification, dissolution, uniformity of dosage units, assay, related substances, loss on drying, residual solvents and microbiological quality. The specifications are adequate to control the medicinal product.
All analytical methods used to test the drug product have been properly described. All non-pharmacopoeial methods were validated.
Satisfactory batch data have been provided and the results comply with the specification and confirm consistency of the product.

Stability of the Product
ICH compliant stability studies in accelerated (40 ± 2 °C/75 ± 5 % RH) and long-term storage conditions (25 ± 2 °C/60 ± 5 % RH) have been performed up to 6 months and 12 months, respectively. The parameters tested were: appearance, loss on drying, dissolution, related substances, assay and microbiological purity. The proposal to extrapolate this data to 24 months shelf life is acceptable.

Comparability Exercise for Drug Product
Compatibility of the formulation with the proposed container closure system was demonstrated by the ongoing stability studies.

2.3 Non-Clinical aspects

Since Raloxifene Teva is essentially similar product to reference product, no additional safety and toxicology studies were considered necessary.

Discussion on Non-Clinical aspects

Raloxifene is a Selective Oestrogen Receptor Modulator (SERM). Raloxifene's biological actions, like those of oestrogen, are mediated through high affinity binding to oestrogen receptors and regulation of gene expression. The non-clinical overview considered in detail aspects of the effects of raloxifene which are not directly relevant to the proposed therapeutic indication.

2.4 Clinical Aspects

Introduction

The initial CHMP assessment addressed pharmacokinetic data in respect of one bioequivalence study (study XX) and one study investigating intra-subject variability (study YY). However, using the standard 80.00 to 125.00 criteria bioequivalence was not demonstrated. The applicant provided a new study (study ZZ) to provide evidence of acceptable bioequivalence.

It is stated that all clinical work has been conducted in compliance with Good Clinical Practices (GCP) as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Clinical studies

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic bioavailability studies. New clinical studies are neither required nor submitted. Bioequivalence between the test product and the reference product has been investigated in two cross-over study after a single dose in fasting conditions of the 60 mg film coated tablet (Study XX and ZZ). The second study (Study YY) was to investigate intra-subjects variability.

Pharmacokinetics

Study XX

Methods

Study design

Study XX was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to evaluate the comparative bioavailability of two formulations of raloxifene administered to healthy, male and post-menopausal and/or surgically sterile female subjects under fasting conditions.

The study products were administered as a single oral dose of 1 x 60 mg tablets of either the test or reference formulation with 240 ml of water, after an overnight fast of at least 10 hours prior to drug administration and for at least 4 hours following drug administration. The study consisted of 2 treatment phases of 120 hours. Patients were recruited in 2 groups of 40, for logistical ease. There was a 14 day washout period between the treatments.

In each period, 29 blood samples from 28 time points were obtained from an arm vein of each subject by direct veno puncture or from an indwelling cannula. During each study period, blood samples (1 x 6 ml each) were taken from each subject at pre-dose and after dose administration at 0.33, 0.67, 1, 2, 3, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.33, 6.67, 7, 8, 9, 10, 12, 15, 18, 24, 36, 48, 72, 96 and 120 hours.

This study was performed by qualified investigators in a clinical facility located in Canada. The clinical laboratory facility was also located in Canada.. The Analytical, Pharmacokinetic, Statistical and Report Issuing facility was also located in Canada.

The clinical study protocol No XX was approved by the Ethics Committee on 24/04/2008. The clinical phase was performed in two groups and two periods. Subjects of group 1 were tested on 08/05/2008 and 22/05/2008 (period 1 and 2 respectively). Subjects of group 2 were tested on 11/05/2008 and 25/05/2008 (period 1 and 2 respectively). The analysis of the samples was conducted in the period from 28/05/2008 to 30/05/2008 for group 1 and in the period from 30/05/2008 to 02/06/2008 for group 2.

The study was complying with GCP, as claimed by the applicant.

Test and reference products

Raloxifene 60 mg Tablets by Teva Pharmaceutical Industries Ltd (manufacturing Date: Feb. 10, 2008) has been compared to Evista® 60 mg Film Coated Tablets by Eli Lilly and Company Limited, UK (exp. date 10 2008).

Population(s) studied

Eighty subjects were recruited, and 79 subjects who completed the study were included in the pharmacokinetic and statistical analysis. Subject 28 was excluded from the study at Period 2 check-in due to non-compliance. There were 61 male between age of 18 – 55 years and 18 were post-menopausal and/or surgically sterile female subjects between age of 18 – 65 years. All subjects were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination

Analytical methods

Raloxifene was measured in plasma using a validated chromatographic assay method (LC-MS/MS method), with a lower limit of quantification of 0.0100 ng/ml. The sample analysis calibration standards range was from 0.0100 to 1.50 ng/ml. The validation of the analytical method is satisfactory.

Pharmacokinetic Variables

The pharmacokinetic parameters AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el} and $T_{1/2}$ were estimated based on plasma raloxifene levels for each subject included in the statistical analysis.

Statistical methods

Descriptive statistics were estimated for the pharmacokinetic parameters in each treatment. Analysis of variance (ANOVA) was applied to log-transformed AUC_t, AUC_{inf}, C_{max} and to untransformed K_{el} and $T_{1/2}$ parameters. The significance of the sequence, period, treatment, and subject within- sequence effects were tested. The least square means, the differences between the treatments least square means, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated. Values for the T_{max} parameter were analyzed by a non-parametric approach.

Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:
• The 90% confidence intervals of the relative mean plasma raloxifene AUC_t and AUC_{inf} of the test to reference products should be between 80-125%.
• The 90% confidence interval of the relative mean plasma raloxifene C_{max} of the test to reference products should be between 75-133%.
The Applicant claimed that the widening of the bioequivalence range for raloxifene is justified due to the following:
1) High variability of the drug:
In-house data indicates that the C_{max} intra-subject coefficient of variation for Evista® is greater than 30%.
2) Evidence demonstrating that raloxifene's efficacy is not related to C_{max}, and by the drug's proven safety at relatively high doses:

a. Efficacy: Administration of raloxifene with a standardized high fat meal increases C_{max} by 28%. Despite this difference, the product monograph for raloxifene (Evista®) states that the drug can be given either with or without food, indicating that the efficacy of the drug is not related to its C_{max}.

b. Safety: A large, multinational placebo-controlled trial assessed the safety of 60 mg and 120 mg daily doses of raloxifene in over five thousand post-menopausal women for 36 months. The majority of adverse events that occurred during the study were mild, and generally did not require discontinuation of therapy.

Safety was assessed based on the severity and causality of adverse events experienced by subjects who underwent drug administration.

Results

Table 1. Pharmacokinetic parameters

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test (means (CV%))	9.1732 (57)	10.2624 (54)	0.2763 (67)	8.51 (88)	28.15 (63)
Reference (means (CV%))	9.9682 (63)	10.9808 (64)	0.3176 (64)	7.32 (86)	26.62 (71)
***Ratio (90% CI)**	86.96 – 98.40	88.37 – 100.55	79.96 – 97.88		
Intra subject CV (%)	23.62	24.55	39.59		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

**ln-transformed values*

No serious Adverse Events (AEs) were reported during the conduct of this study. A total of 51 AEs in 26 subjects experienced over the course of the study. The AEs were mild in severity. A total of 33 AEs were reported following the administration of Test product and the most common AEs were blood creatinine increase (in 3 subjects), haemoglobin decrease (in 3 subjects) and haematocrit decrease (in 3 subjects). A total of 18 AEs were reported following the administration of Evista® and the most common AE was headache (in 3 subjects).

- Conclusions

The 90% confidence interval of the relative mean raloxifene C_{max} of the test to reference product is outside the 80-125% range.

Study YY

Methods

Study design

Study YY was an open-label, two-period, single-treatment study, designed to estimate the intra-subject variability of the pharmacokinetic parameters AUC_t, AUC_{inf} and C_{max} for Evista® after single-dose administration to healthy female subjects under fasting conditions.

Subjects were given a single dose of Evista® (raloxifene hydrochloride) 60 mg Tablets on two separate occasions under fasting conditions. In each period, an optional pre-study snack was provided to each subject after check-in and prior to fasting. Subjects fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration. The washout interval between successive drug administrations was 14 days.

This study was performed by qualified investigators in a clinical facility located in Canada. The clinical laboratory facility was also located in Canada. The Analytical, Pharmacokinetic, Statistical and Report Issuing facility was also located in Canada.

The clinical study protocol No YY was approved by the Ethics Committee on 14/02/2008. The clinical phase was performed in two periods. Subjects in period 1 were tested on 23/02/2008 and in period 2 on 08/03/2008. The analysis of the samples was conducted on 14/03/2008 and 19/03/2008 for period 1 and 2 respectively.

The study was complying with GCP, as claimed by the applicant.

Test and reference products

The Test product was Evista® 60 mg Tablets (Eli Lilly and Company Ltd., UK), e*xpiration Date:* 10-2008

Population(s) studied

The study population included 16 non-smoking, post-menopausal and/or surgically sterile female volunteers between 18-65 years of age with a BMI between 19 and 30, who were judged to be healthy based on a medical history, ECG, laboratory evaluation and physical examination. 14 subjects completed the study were included in the pharmacokinetic and statistical analysis. Subject 15 was excluded from the study after Period 1 dosing due to an adverse event (vomiting) and Subject 7 was excluded from the study prior to Period 2 check-in due to non-compliance. All the 16 subjects were included in the safety analysis.

Analytical methods

Plasma concentrations of raloxifene were measured by validated analytical methods (LC-MS/MS method). Concentrations of raloxifene were measured from the samples collected over a 120-hour interval after dosing in each period. Protocol deviations were minor one and related to washout period, or samples were collected with one minute difference from the pre-specified time.

Pharmacokinetic Variables

Based on plasma raloxifene data the intra-subject variability of the pharmacokinetic parameters AUC_t, AUC_{inf} and C_{max} was estimated.

Statistical methods

Descriptive statistics were estimated for the pharmacokinetic parameters in each treatment. Analysis of variance (ANOVA) was applied to log-transformed AUC_t, AUC_{inf} and C_{max} and to untransformed K_{el} and $T_{1/2}$ parameters. The significance of the period and subject effects were tested. The least square means, the differences between the period least square means and the corresponding standard errors were estimated for log-transformed AUC_t, AUC_{inf} and C_{max} parameters. Based on these statistics, the ratios of the geometric means for each period and the corresponding 90% confidence intervals were calculated. Values for the T_{max} parameter were analyzed by a non-parametric approach.

Results

Table 1. Pharmacokinetic parameters

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Period 1 (mean (CV%))	15.7657 (33)	17.5986 (37)	0.3899 (37)	5.38 (32)	30.38(43)
Period 2 (mean (CV%))	15.5902 (37)	17.7494 (38)	0.4093 (54)	7.65 (73)	37.73 (88
***Ratio (90%CI)**	94.87 – 111.37	90.92 – 107.92	83.33 – 124.02		
CV (%)	12.03	12.86	30.37		

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$T_{1/2}$	half-life

**ln-transformed values*

No serious AEs were reported during the conduct of this study.
None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results

- Conclusions

The estimated intra-subject coefficient of variation of plasma raloxifene for AUC_t is 12.03%, for AUC_{inf} is 12.86% and for C_{max} is 30.37%.

Study *ZZ*

Methods

Study design

Study ZZ was a two-treatment, four-period, replicate-design crossover study in the fasted state, designed to demonstrate the bioequivalence of Raloxifene 60 mg Tablets (Teva Pharmaceutical Industries Ltd.) with the reference product, Evista® 60 mg Film Coated Tablets (Daiichi Sankyo UK Ltd., UK).

The study products were administered as a single oral dose of 1 x 60 mg tablets of either the test or reference formulation after an overnight fast of at least 10 hours prior to drug administration. The study consisted of 4 treatment periods. Patients were recruited in 2 groups. There was a 14 day washout period between the treatments.

In each period, 25 blood samples from 24 time points were obtained. Each sample was 6 ml. Blood samples were collected at: 0(x2), 1, 2, 3, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96, and 120 hours. The washout between the start of each period was 2 weeks.

This study was performed by qualified investigators in a clinical facility located in Canada. The clinical laboratory facility was also located in Canada. The Analytical, Pharmacokinetic, Statistical and Report Issuing facility was also located in Canada.

The clinical study protocol No ZZ was approved by the Ethics Committee on 23/07/2009. Amended study protocol was approved by the Ethics Committee on 28/07/2009.
The clinical phase was performed in two groups and 4 periods. Subjects of group 1 were tested on 01/08/2009, 15/08/2009, 29/08/2009 and 12/09/20097 (periods 1,2,3 and 4 respectively). Subjects of group 2 were dosed on 23/08/2009, 6/09/2009, 20/09/2009 and 4/10/2009 (period 1,2,3 and 4 respectively). The analysis of the samples was conducted in the period from 18/09/2009 to 28/09/2009 for group 1 and in the period from 13/10/2009 to 15/10/2009 for group 2.

The study was complying with GCP, as claimed by the applicant.

Test and reference products

Raloxifene 60 mg Tablets, (Teva Pharmaceutical Industries Ltd.) Manufacturing Date: Feb. 10, 2008 has been compared to Evista® 60 mg Film Coated Tablets, (Daiichi Sankyo UK Ltd., UK) Expiration Date: 10 2011.

Population(s) studied

The study enrolled 60 individuals who were randomised to sequences of either TRTR or RTRT (where T denotes test and R denotes reference) and any subjects who completed both a test and reference period were included in the analysis. Subject 04 was dismissed from the study prior to Period 4 dosing due to adverse events (out of range mid-study haematology test results). Subject 51 voluntarily withdrew from the study prior to Period 4 check-in due to an adverse event (feeling tired)
Subject 31 voluntarily withdrew from the study prior to Period 4 check-in for personal reasons. These subjects were included in the analysis. Subject 15 was dismissed from the study after Period 2 dosing due to adverse events (vomiting and loose stool). Measurements were taken up to 48 hours. The subject has been randomised to the TRTR sequence The study population included non-smoking and/or light-smoking, post-menopausal and/or surgically sterile female volunteers from 18 to 65 years of age, with a BMI from 19 to 30, who were judged to be healthy based on a medical history, ECG, laboratory evaluation, and physical examination.

Analytical methods

Raloxifene concentrations were measured from plasma by a validated analytical method. Subject plasma concentrations of Raloxifene were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method Plasma samples were assayed for raloxifene according to the principles of Good Laboratory Practice.
The validation of the analytical method is satisfactory.

Deviations in blood sampling times of more than 1 minute were reported. Deviations from the scheduled sampling time were accounted for in the pharmacokinetic calculations since the actual sampling times were used.

Pharmacokinetic Variables

AUCt, AUCinf, Cmax, Tmax, Kel, and Thalf were estimated based on raloxifene plasma levels for each subject included in the data set.

Statistical methods

Descriptive statistics were estimated for the pharmacokinetic parameters in each treatment. A mixed model was applied to log-transformed AUC_t, AUC_{inf}, C_{max} and ANOVA to untransformed K_{el} and $T_{1/2}$ parameters. The significance of the group, sequence-within-group, period within- group, treatment, and treatment-within-group interaction were tested.

The standard bioequivalence approach was followed in this study. The treatment least-squares means, the differences between the treatment least-squares means, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, and C_{max} parameters were calculated. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated. Values for the T_{max} parameter were analyzed by a non-parametric approach.

The Applicant stated that: *"Since the within-subject variability for C_{max} of the reference product was ≥30%, the following criteria were used to evaluate the bioequivalence between the test and reference products"*:

• The 90% confidence intervals of the relative mean AUC_t of the test to reference products should be between 80% and 125%.
• The 90% confidence intervals of the relative mean C_{max} of the test to reference products should be between 75% and 133%.

Safety was assessed based on the severity and causality of adverse events experienced by subjects who underwent drug administration.

Results

Table 1. Pharmacokinetic parameters

Summary-Conclusions:
Pharmacokinetic Results:

Analyte: Raloxifene (Treatment A1, N= 59; Treatment A2 N = 57; Treatment B1 & B2, N= 58)

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic	(CV%)	Geometric			Lower	Upper	
Based on Measured Data									
AUCt *(ng*h/mL)*	A1	15.9432	(51)	14.3621	A vs. B	87.06	83.63	90.63	20
	A2	15.6432	(44)						
	B1	17.1586	(41)	16.4973					17
	B2	18.6219	(49)						
AUCinf *(ng*h/mL)*	A1	17.6515	(51)	15.7860	A vs. B	89.23	85.52	93.11	21
	A2	17.3494	(47)						
	B1	18.5922	(42)	17.6908					18
	B2	19.8582	(49)						
Cmax *(ng/mL)*	A1	0.5156	(94)	0.4205	A vs. B	84.49	78.23	91.26	41
	A2	0.5401	(68)						
	B1	0.5502	(61)	0.4976					32
	B2	0.6526	(76)						
Tmax *(h)*	A1	6.40	(68)	For each pharmacokinetic parameter: • The first two lines present data for Treatment A, first instance (A1) and second instance (A2) • The last two lines present data for Treatment B, first instance (B1) and second instance (B2)					
	A2	8.00	(108)						
	B1	5.95	(36)						
	B2	6.60	(90)						
Kel *(1/h)*	A1	0.0283	(34)						
	A2	0.0287	(37)						
	B1	0.0290	(32)						
	B2	0.0300	(28)						
Thalf *(h)*	A1	29.17	(61)						
	A2	29.35	(59)						
	B1	27.13	(43)						
	B2	25.45	(34)						

There were no deaths or other serious AEs reported during the study. Subjects 04, 15 & 51 were withdrawn due to adverse events.

- Conclusions

The 90% confidence interval of the relative mean raloxifene C_{max} of the test to reference product is within the 75-133% range.

Based on the presented bioequivalence study Raloxifene Teva is considered bioequivalent with Evista® 60 mg Film Coated Tablets.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified.

Discussion on Clinical aspects

The overall design of the two initially submitted studies for this application is appropriate and the results have demonstrated bioequivalence for AUCs. However, in study XX the applicant selected a wider range for C_{max} (75 – 133%). The justification presented was based on the demonstration of high intra-subject variability of the drug in Study YY as claimed by applicant. However, the estimated intra-subject coefficient of variation of plasma raloxifene for AUC_t was 12.03%, for AUC_{inf} 12.86% and for C_{max} 30.37%. No confidence interval was given and it cannot be concluded that the drug is highly variable. Furthermore the two studies conducted were carried out on two different populations and the assumption of high variability can not be extrapolated to the pivotal bioequivalence study. Therefore using the 80-125% CI for C_{max} showed that that the product failed to demonstrate bioequivalence with the reference product Evista®. The applicant conducted a new bioequivalence study (study ZZ) in order to address major concern. The applicant provided an acceptable trial design to demonstrate high variability and thus justify the widening of the acceptance limits to 75 – 133% for Cmax. The results of a new study excluded one subject from the estimation of C_{max}, despite this subject provided data on C_{max} for the first 2 periods. The applicant was requested to repeat the analysis for C_{max} including subject 15. The inclusion of the data for Subject 15 changed the ratio for C_{max} from 84.49% (CI 78.23 - 91.26%) to 83.75% (CI 77.49 - 90.51%) which was still within the pre-specified CI of 75% - 133%. Therefore this has not altered final conclusion of bioequivalence.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and clinical data has been shown. A benefit/Risk ratio comparable to the reference product can therefore be concluded.

Recommendation

Based on the CHMP review of available data, the CHMP considered majority decision that the benefit/risk ratio of Raloxifene Teva in the treatment of treatment and prevention of osteoporosis in postmenopausal women was favourable and therefore recommended the granting of the marketing authorisation.