Public Assessment Report

Decentralised Procedure

Raloxifene Hydrochloride Actavis 60mg Film-coated Tablets

(Raloxifene hydrochloride)

Procedure No: UK/H/5551/001/DC

UK Licence No: PL 30306/0519

Actavis Group PTC ehf
LAY SUMMARY

Raloxifene Hydrochloride Actavis 60mg Film-coated Tablets
(Raloxifene hydrochloride, film-coated tablets, 60 mg)

This is a summary of the Public Assessment Report (PAR) for Raloxifene Hydrochloride Actavis 60mg Film-coated Tablets (PL 30306/0519; UK/H/5551/01/DC). It explains how Raloxifene Hydrochloride Actavis 60mg Film-coated Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Raloxifene Hydrochloride Actavis 60mg Film-coated Tablets.

This product will be referred to as Raloxifene Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Raloxifene Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Raloxifene Tablets and what are they used for?
Raloxifene Tablets is a ‘generic medicine’. This means that Raloxifene Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH; EU/1/98/073/001-004).

Raloxifene Tablets are used to treat and prevent osteoporosis in postmenopausal women. Raloxifene Tablets reduce the risk of vertebral fractures in women with postmenopausal osteoporosis. A reduction in the risk of hip fractures has not been shown.

How do Raloxifene Tablets work?
Raloxifene Tablets contain the active substance raloxifene hydrochloride, which belongs to a group of non-hormonal medicines called Selective Oestrogen Receptor Modulators (SERMs).

When a woman reaches the menopause, the level of the female sex hormone oestrogen goes down. Raloxifene Tablets mimic some of the helpful effects of oestrogen after the menopause. Osteoporosis is a disease that causes the patient’s bones to become thin and fragile - this disease is especially common in women after the menopause. Although it may have no symptoms at first, osteoporosis makes the patient more likely to break bones, especially in the patient’s spine, hips and wrists and may cause back pain, loss of height and a curved back.

How are Raloxifene Tablets used?
The pharmaceutical form of Raloxifene Tablets is a tablet and the route of administration is oral.

The patient must always take Raloxifene Tablets exactly as their doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure.

The dose is one tablet a day. It does not matter what time of day the patient takes their tablet but taking the tablet at the same time each day will help the patient to remember to take it. The patient may take it with or without food.

The patient should swallow the tablet whole. If the patient wishes, the patient may take a glass of water with it. The patient must not break or crush the tablet before taking it. A broken or crushed tablet may taste bad and there is a possibility that the patient will receive an incorrect dose.

The patient’s doctor will tell the patient how long they should continue to take Raloxifene Tablets. The
doctor may also advise the patient to take calcium and vitamin D supplements.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Raloxifene Tablets have been shown in studies?**
As Raloxifene Tablets is a generic medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Raloxifene Tablets?**
Because Raloxifene Tablets is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with Raloxifene Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why was Raloxifene Tablets approved?**
It was concluded that, in accordance with EU requirements, Raloxifene Tablets have been shown to have comparable quality and to be bioequivalent to Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH). Therefore, the MHRA decided that, as for Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH) the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Raloxifene Tablets?**
A risk management plan (RMP) has been developed to ensure that Raloxifene Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Raloxifene Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Raloxifene Tablets**
Greece, Hungary, Ireland and the UK agreed to grant a Marketing Authorisation for Raloxifene Tablets on 24 December 2014. A Marketing Authorisation was granted in the UK on 19 January 2015.

The full PAR for Raloxifene Tablets follows this summary.

For more information about treatment with Raloxifene Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Raloxifene Tablets (PL 30306/00519; UK/H/5551/001/DC) could be approved. The product is a prescription-only medicine (POM) and 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 (see section 5.1 of the Summary of Product Characteristics).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Greece, Hungary and Ireland as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Evista 60 mg film coated tablets, which was originally granted by the Centralised Procedure (CP) on 05 August 1998 to Daiichi Sankyo Europe GmbH (EU/1/98/073/001-004).

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's 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. Data suggests that the oestrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene specific.

One bioequivalence study was submitted to support this application comparing the applicant’s test product Raloxifene Tablets with the reference product Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH; EU/1/98/073/002) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practises (GCP) requirements as referenced in the ICH guidelines (ICH E6), local regulatory requirements and the principles enunciated in the Declaration of Helsinki.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS and CMS considered that the application could be approved at the end of procedure on 24 December 2014. After a subsequent national phase, a licence was granted in the UK on 19 January 2015.
II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 60 mg of the active ingredient raloxifene hydrochloride equivalent to 56 mg raloxifene free base. Other ingredients consist of the pharmaceutical excipients sodium starch glycolate (primogel) type A, citric acid monohydrate, microcrystalline cellulose, dibasic calcium phosphate 2-hydrate, poloxamer 407, magnesium stearate and the tablet coating Opadry OY-LS-28908 (White II) [consisting of titanium dioxide (E171), lactose monohydrate, hypromellose 2910/ hypromellose 15 cP (E464), macrogl 4000, hypromellose 2910/ hypromellose 3cP (E464) and hypromellose 2910/ hypromellose 50 cP (E464). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is packed into blisters of transparent polyvinyl chloride (PVC)/polyethylene (PE)/Polychlorotrifluoroethylene (PCTFE) aluminium foil in pack sizes of 14, 28, 30 or 84 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Raloxifene hydrochloride

Structural formula:

![Structural formula of Raloxifene hydrochloride](image)

Molecular formula: \( C_{28}H_{27}NO_4S \cdot HCl \)
Molecular mass: 510.05 g/mol
Appearance: An almost white or pale-yellow powder.
Solubility: Very slightly soluble or practically insoluble in water and acetone, slightly soluble in ethanol (96 % v/v).

Raloxifene hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, raloxifene hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing 60 mg raloxifene (as the hydrochloride) per tablet that are bioequivalent to the reference product Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH). A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and *in-vitro* dissolution profiles have been provided for the proposed and originator product.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the tablet film coat Opadry OY-LS-28908 (White II) which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation on future commercial-scale batches.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 4 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.
II.5  Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Raloxifene Tablets is presented below:
<table>
<thead>
<tr>
<th>Actavis</th>
<th>Actavis</th>
<th>Actavis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene 60mg Hydrochloride Film-coated Tablets</td>
<td>Raloxifene 60mg Hydrochloride Film-coated Tablets</td>
<td>Raloxifene 60mg Hydrochloride Film-coated Tablets</td>
</tr>
<tr>
<td>Actavis</td>
<td>Actavis</td>
<td>Actavis</td>
</tr>
<tr>
<td>---------</td>
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<td>---------</td>
</tr>
<tr>
<td>Raloxifene 60mg Hydrochloride Film-coated Tablets</td>
<td>Raloxifene 60mg Hydrochloride Film-coated Tablets</td>
<td>Raloxifene 60mg Hydrochloride Film-coated Tablets</td>
</tr>
</tbody>
</table>
III  NON-CLINICAL ASPECTS

III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of raloxifene are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3  Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4  Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5  Ecotoxicity/environmental risk assessment (ERA)
Since Raloxifene Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6  Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1  Introduction
The clinical pharmacology of raloxifene is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of raloxifene.

Based on the data provided, Raloxifene Tablets can be considered bioequivalent to Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH).
IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, randomised, single dose, four-way replicate crossover study to compare the pharmacokinetics of the applicant’s test product Raloxifene Tablets (Actavis Group PTC ehf) versus the reference product, Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH), in healthy adult subjects under fasting conditions.

The subjects were administered a single dose (60 mg) of either the test or the reference product with 240 ml of water, after an overnight fast.

Blood samples were collected before and up to and including 144 hours after each administration. The parent compound raloxifene and the metabolites raloxifene-4’-glucuronide and raloxifene-6’-glucuronide were analysed. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below:

Table: Pharmacokinetic parameters for the parent compound raloxifene (non-transformed values; arithmetic mean ± SD, tmax median, range).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ pg/ml/h</th>
<th>AUC$_{0-\infty}$ pg/ml/h</th>
<th>C$_{\text{max}}$ pg/ml</th>
<th>t$_{\text{max}}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>14145.39 ± 6652.44</td>
<td>15375.97 ± 7438.85</td>
<td>443.69 ± 280.14</td>
<td>5.25 (0.5 – 48.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>13973.70 ± 6441.32</td>
<td>15152.24 ± 6910.83</td>
<td>457.93 ± 305.75</td>
<td>5.25 (0.50 – 72.0)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>94.76 – 106.40%</td>
<td>94.60 – 106.29%</td>
<td>88.25 – 106.49%</td>
<td></td>
</tr>
</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{\text{max}}$ maximum plasma concentration
t$_{\text{max}}$ time until C$_{\text{max}}$ is reached

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC, and C$_{\text{max}}$ values for the parent compound raloxifene lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Raloxifene
A summary table of safety concerns as approved in RMP is listed as follows:

### Summary table of Safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Venous thromboembolism, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis and superficial vein thrombophlebitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Flu syndrome</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Increase in serum triglycerides</td>
</tr>
<tr>
<td></td>
<td>Endometrial cancer (SERM class-effect)</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in patients with hepatic insufficiency</td>
</tr>
<tr>
<td></td>
<td>Use in patients with severe renal impairment</td>
</tr>
<tr>
<td></td>
<td>Use in patients with breast cancer</td>
</tr>
<tr>
<td></td>
<td>Concomitant use with SERMs, oestrogens or other medications with oestrogenic/ anti-oestrogenic actions</td>
</tr>
</tbody>
</table>

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

### Summary table of Risk Minimisation Measures

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism, including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis and superficial vein thrombophlebitis</td>
<td>Proposed text in SmPC Section 4.3: listed contraindications Section 4.4: warning regarding the risk for venous thromboembolic events, patients at risk, drug discontinuation and reinitiating of treatment if considered needed Section 4.8: listed reactions Proposed text in PIL (Annex 2)</td>
<td>None</td>
</tr>
<tr>
<td>Stroke</td>
<td>Proposed text in SmPC Section 4.4: warning regarding the risk of</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>stroke and the incidence of the reaction</td>
<td><em>Section 4.8: listed reaction</em></td>
<td>None</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>Proposed text in SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>Proposed text in SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Increase in serum triglycerides</td>
<td>Proposed text in SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Endometrial cancer (SERM class-effect)</td>
<td>Proposed text in SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Use in patients with hepatic insufficiency</td>
<td>Proposed text in SmPC</td>
<td>None</td>
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</tr>
<tr>
<td>Use in patients with breast cancer</td>
<td>Proposed text in SmPC</td>
<td>None</td>
</tr>
</tbody>
</table>
The RMP for Raloxifene Tablets adequately documents the safety concerns for the product. Routine pharmacovigilance and risk minimisation are sufficient for the safety concerns in the RMP, given the established benefit-risk profile of raloxifene and the information available to inform decisions on the balance of benefits and risks when it is used in clinical practice.

IV.7 Discussion on the clinical aspects
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Raloxifene Tablets and the reference product Evista 60 mg film coated tablets (Daiichi Sankyo Europe GmbH), under fasting conditions.

The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with raloxifene is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.