Public Assessment Report

Decentralised Procedure

Pioglitazone Hydrochloride 30 mg and 45 mg Tablets

(Pioglitazone hydrochloride)

UK/H/5114/002-03/DC

UK licence no: PL 29831/0528-9

Wockhardt UK Ltd
LAY SUMMARY

On 22nd July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) to Wockhardt UK Ltd for the medicinal products Pioglitazone hydrochloride 30 mg and 45 mg Tablets (PL 29831/0528-29, UK/H/5114/002-03/DC). These are prescription-only medicines (POM).

Pioglitazone Tablets contains pioglitazone. It is an anti-diabetic medicine used to treat type 2 (non-insulin dependent) diabetes mellitus, when metformin is not suitable or has failed to work adequately. This is the diabetes that usually develops in adulthood.

Pioglitazone Tablets helps control the level of sugar in the blood in patients that have type 2 diabetes by helping the body make better use of the insulin it produces. The doctor will check whether Pioglitazone Tablets is working 3 to 6 months after the treatment has started.

Pioglitazone Tablets may be used on its own in patients who are unable to take metformin, and where treatment with diet and exercise has failed to control blood sugar or may be added to other therapies (such as metformin, sulphonylurea or insulin) which have failed to provide sufficient control in blood sugar.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pioglitazone hydrochloride 30 mg and 45 mg Tablets outweigh the risks. Hence Marketing Authorisations have been granted.
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## Module 1
### Information about the initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Pioglitazone hydrochloride 30 mg and 45 mg Tablets</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Pioglitazone hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>30 mg and 45 mg Tablets</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Wockhardt UK Ltd Ash Road North Wrexham LL13 9UF UK</td>
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<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Republic of Ireland</td>
</tr>
<tr>
<td><strong>Procedure Numbers</strong></td>
<td>UK/H/5114/002-3/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 9th June 2013</td>
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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) consider that the applications for Pioglitazone hydrochloride 30 mg and 45 mg Tablets for the following indications were approved.

Pioglitazone is indicated as second or third line treatment of type 2 diabetes mellitus as described below:

as **monotherapy**
- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as **dual oral therapy** in combination with
- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

as **triple oral therapy** in combination with
- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.
- Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended for Pioglitazone hydrochloride 30 mg and 45 mg Tablets, claiming to be generic medicinal products of Actos 30 mg and 45 mg tablets (EU/1/00/150), which were first licensed to Takeda Global Research and Development Centre, on 13th October 2000 via a Centralised procedure.

With UK as the RMS in these Decentralised Procedures (UK/H/5114/002-03/DC), Wockhardt UK Ltd applied for the Marketing Authorisations for Pioglitazone hydrochloride 30 mg and 45 mg Tablets in the Republic of Ireland.

No new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.
A bioequivalence study (single-dose) was submitted to support these applications, comparing the applicant’s test product Pioglitazone hydrochloride 45 mg tablet (Wockhardt Limited, India) with the reference product Actos® 45 mg tablet (Takeda Global Research and development center, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

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 or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification for non-submission of a Risk Management Plan has been provided.

All member states agreed to grant licences for the above products at the end of procedure (Day 210 – 9th June 2013). After a subsequent national phase, the UK granted licences for these products on 22nd July 2013 (PL 29831/0528-29).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Pioglitazone hydrochloride 30 mg and 45 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Pioglitazone hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins; ATC code: A10BG03.</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Tablet, 30 mg and 45 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedures</td>
<td>UK/H/5114/002-03/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Republic of Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 29831/0528-29</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Wockhardt UK Ltd</td>
</tr>
<tr>
<td></td>
<td>Ash Road North</td>
</tr>
<tr>
<td></td>
<td>Wrexham</td>
</tr>
<tr>
<td></td>
<td>LL13 9UF</td>
</tr>
<tr>
<td></td>
<td>UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
DRUG SUBSTANCE
INN: Pioglitazone Hydrochloride

Chemical Names: (5RS)-5-[4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzyl]-1,3-thiazolidine-2,4-dione hydrochloride.

Structure:

![Pioglitazone Hydrochloride structure](image)

Molecular Formula: \(C_{19}H_{21}N_2O_3\text{SCl}\)

Molecular Weight: 392.9 g/mol

Appearance: White to off-white powder

Solubility: The substance is soluble in methanol.

The drug substance is the subject of an active substance master file (ASMF).

Synthesis of the drug 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.

Appropriate proof of structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients carboxymethylcellulose calcium, hydroxypropyl cellulose, lactose monohydrate and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical Development
The objective of the development programme was to formulate robust and stable tablets that contain the same active ingredient as Actos 30 mg and 45 mg tablets (Takeda Global Research and Development Centre, UK).

Comparative impurity and dissolution profiles have been presented for the test and reference products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using the minimum commercial scale batch sizes and has shown satisfactory results. The applicant has committed to perform further process validation on three full scale commercial-scale batches of each tablet strength post approval.

Finished Product Specification
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in aluminium/aluminium blisters with packs of 28, 56 and 84 tablets. Not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with no special storage conditions are set. These are satisfactory.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert report/Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of pioglitazone hydrochloride are well known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an environmental risk assessment. This was satisfactory.

There are no objections to the approval of these products from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of these applications, the following bioequivalence study has been submitted:

This is an open label randomised, single dose, two-treatment, two period, two sequence, comparative bioavailability study of Pioglitazone hydrochloride 45 mg tablet (Wockhardt Limited, India) versus the reference product Actos® 45 mg tablet (Takeda Global Research and development center UK) in healthy adult male human subjects under fasting conditions.

Blood samples were taken at pre-dose and the following time points: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 9.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours post dose in each period. There was a washout period of 12 days between the two periods.
The plasma concentrations of Pioglitazone and Hydroxypioglitazone (M-IV) were determined by a validated LC-MS/MS method.

**Geometric Means, Ratios and 90% Confidence Interval for Pioglitazone (n=48) on Log transformed Data**

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio %</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1765.14</td>
<td>1871.29</td>
<td>94.33</td>
<td>86.04 – 103.42 %</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng.hr/mL)</td>
<td>19360.59</td>
<td>20082.29</td>
<td>96.41</td>
<td>89.53 – 103.81 %</td>
</tr>
</tbody>
</table>

**Geometric Means, Ratios and 90% Confidence Interval for Hydroxypioglitazone (M-IV) (n=48) on Log transformed Data**

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>Test</th>
<th>Reference</th>
<th>Ratio %</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1005.37</td>
<td>1063.17</td>
<td>94.56</td>
<td>87.67 – 101.98 %</td>
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<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (ng.hr/mL)</td>
<td>46302.22</td>
<td>49222.14</td>
<td>94.07</td>
<td>87.63 – 100.98 %</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for C<sub>max</sub>, AUC<sub>0-1</sub> and AUC<sub>0-72</sub> were within the pre-defined limits acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Pioglitazone hydrochloride 45 mg tablets) and the reference formulation (Actos® 45 mg tablets) for Pioglitazone and its metabolite Hydroxypioglitazone (M-IV).

Satisfactory justification is provided for a bio-waiver for the applicant’s lower strength tablets. As Pioglitazone hydrochloride 30 mg and 45 mg Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**), the results and conclusions of the bioequivalence study for 45 mg formulation can be extrapolated to the other strength, i.e. 30 mg Tablets.

**Pharmacodynamics**
No new data have been submitted and none are required for applications of this type.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.
Expert Report
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products.

Marketing Authorisation Application (MAA) Forms
The MAA forms are medically satisfactory.

Conclusion
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Pioglitazone hydrochloride 30 mg and 45 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of these type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Pioglitazone hydrochloride 45 mg tablets and the reference product, Actos® 45 mg tablets. As Pioglitazone hydrochloride 30 mg and 45 mg Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr*), the results and conclusions of the bioequivalence study for 45 mg formulation can be extrapolated to the other strength i.e. 30 mg Tablets.

No new or unexpected safety concerns arose from these applications.

The SmPCs and PIL are satisfactory and consistent with those of the reference products, where appropriate. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with pioglitazone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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