Public Assessment Report

Decentralised Procedure

Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets

(metformin hydrochloride)

Procedure No: UK/H/5957/001-3/DC

UK Licence No: PL 29831/0655-0657

Wockhardt UK Ltd
LAY SUMMARY
Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets (metformin hydrochloride)

This is a summary of the public assessment report (PAR) for Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets (PL 29831/0655-0657: UK/H/5957/001-3/DC). This product will be referred to as Yaltormin SR Tablets in the remainder of this summary, for ease of reading.

This summary explains how Yaltormin SR Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use these products.

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

What are Yaltormin SR Tablets and what are they used for?
Yaltormin SR Tablets are ‘generic medicines’. This means that Yaltormin SR Tablets are similar to ‘reference medicines’ already authorised in the UK called Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets (Merck Sero Limited; PL 11648/0054 & 0066-0067).

Yaltormin SR tablets are used for the treatment of Type 2 (non-insulin dependent) diabetes mellitus when diet and exercise changes alone have not been enough to control blood glucose (sugar). Insulin is a hormone that enables body tissues to take glucose from the blood and to use it for energy or for storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood which can cause a number of serious long-term problems so it is important that the patient continue to take the medicine, even though the patient may not have any obvious symptoms. Yaltormin SR makes the body more sensitive to insulin and helps return to normal the way the body uses glucose.

Yaltormin SR tablets are associated with either a stable body weight or modest weight loss.

Yaltormin SR Tablets are specially made to release the drug slowly in the body and therefore are different to many other types of tablet containing metformin.

How are Yaltormin SR Tablets used?
Yaltormin SR Tablets are taken by mouth. A single tablet should be swallowed (without chewing) with a glass of water. The patient should take one or two tablets a day, depending on doctor’s recommendation, with an evening meal.

The maximum recommended daily dose is 2000 milligrams of Yaltormin SR tablet.

Patients will usually start treatment with 500 milligrams of Yaltormin SR daily. The dose may be adjusted by a doctor after about 2 weeks of taking this medicine.

Yaltormin SR Tablets can only be obtained on prescription from a doctor.

For further information on how Yaltormin SR Tablets are used, please see the Summaries of Product Characteristics and the package leaflet available on the MHRA website.

How do Yaltormin SR Tablets work?
Yaltormin SR prolonged release tablets contain the active ingredient metformin hydrochloride which belongs to a group of medicines called biguanides. This medicine works by reducing the amount of
sugar produced in the liver and increases the sensitivity of muscle cells to insulin. This enables the cells to remove sugar from the blood more effectively. As a result, the absorption of sugar from the intestines into the bloodstream is delayed.

**How have Yaltormin SR Tablets been studied?**

Because Yaltormin SR Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the medicinal products, Glucophage SR 750 mg prolonged-release tablet Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets (Merck Serono Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Yaltormin SR Tablets?**

As Yaltormin SR Tablets are generic medicines that are bioequivalent to Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets, their benefits and risks are taken as being the same as Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets.

**Why are Yaltormin SR Tablets approved?**

It was concluded that, in accordance with EU requirements, Yaltormin SR Tablets have been shown to have comparable quality and to be bioequivalent to Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets. Therefore, the view was that, as for Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Yaltormin SR Tablets?**

A risk management plan has been developed to ensure that Yaltormin SR Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Yaltormin SR Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Yaltormin SR Tablets**

Republic of Ireland and the UK agreed to grant Marketing Authorisations for Yaltormin SR Tablets on 01 March 2016. Marketing Authorisations were granted in the UK on 15 March 2016.

The full PAR for Yaltormin SR Tablets follows this summary. For more information about treatment with Yaltormin SR Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy the Member States considered that the applications for Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets (PL 29831/0655-0657: UK/H/5957/001-3/DC) are approvable. The products are prescription-only medicines (POM) indicated for the treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Yaltormin SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Republic of Ireland as Concerned Member State (CMS). The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets, which were authorised to Merck Serono Limited (PL 11648/0054 & 0066-0067) on 26 November 2004, 21 February and 16 September 2008 respectively.

The medicinal product contains the active substance, metformin hydrochloride. Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

With the exception of the bioequivalence studies, 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. Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release 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.

Both Member States agreed to grant Marketing Authorisations for the above products at the end of the procedure (Day 202 – 01 March 2016). After a subsequent national phase, the UK granted Marketing Authorisations (PL 29831/0655-0657) for these products on 15 March 2016.
II QUALITY ASPECTS

II.1 Introduction

The products are prolonged release tablets. Each prolonged release tablet contains 500 mg, 750 mg or 1000 mg metformin hydrochloride (corresponding to 390 mg, 585 mg or 780 mg metformin base).

Other ingredients consist of the pharmaceutical excipients magnesium stearate, silica colloidal anhydrous, carmellose sodium and hypromellose. Appropriate justification for the inclusion of each excipient has been provided.

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

None of the excipients contain materials of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packed in blister strips composed of aluminium foil and polyvinylchloride (PVC). The pack sizes are 28 and 56 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Metformin Hydrochloride
Chemical name: N,N-Dimethyl imido-dicarbonimidicdiamide *)1,1-Dimethyl Biguanide *)N-N Dimethyl Diguanide *)N’ – Dimethyl guanylguanidine*) as hydrochloride

Structural formula:

![Structural formula of Metformin Hydrochloride](image)

Molecular formula: C$_4$H$_{12}$ClN$_{15}$
Molecular mass: 165.6 g/mol
Appearance: White or almost white crystals.
Solubility: Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol and practically insoluble in acetone and in methylene chloride.

Metformin Hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, metformin hydrochloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate robust, stable prolonged-released tablets that contain the same active ingredient as Glucophage SR 500 mg, 750 mg and 1000 mg prolonged release tablets (Merck Serono Limited).

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

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results. Process validation data on commercial scale batches have been provided.

Finished Product Specifications
The finished product specifications proposed are acceptable. The test methods that have been described 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 Products
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 3 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 these applications from a pharmaceutical point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of metformin are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetic 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 these products are intended for substitution of originator products, 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
There are no objections to the approval of these applications from a non-clinical point of view.

IV CLINICAL ASPECTS
These are generic applications submitted under the Decentralised Procedure according to Article 10.1 of Directive 2001/83/EC, as amended, for Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets.

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of metformin are well known. As metformin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is considered appropriate.

With the exception of the bioavailability studies, no new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of these applications, the Marketing Authorisation Holder has submitted the following five bioequivalence studies:

Study 1
This is an open, randomised, single dose, two-treatment, two-sequence, two-way crossover comparative bioavailability study of Metformin Hydrochloride Extended Release 1000 mg Tablet (test) and Glucophage 1000 mg prolonged release Tablets (reference) in 33 healthy, adult male human subjects under fasting conditions.

Blood samples were collected at 0.00 [pre-dose], 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00, 24.00 and 30.00 hours following drug administration. The washout period was 7 days.

Results
Pharmacokinetic parameters for metformin hydrochloride (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Estimated geometric mean ratio</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
<th>Intra-subject CV%</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>LnCₘₚₓ</td>
<td>101.75</td>
<td>95.17</td>
<td>108.79</td>
<td>16.05</td>
<td>99.95</td>
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<tr>
<td>LnAUC₀₋ₜ</td>
<td>109.54</td>
<td>101.94</td>
<td>117.72</td>
<td>17.30</td>
<td>99.85</td>
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</table>

Conclusion
The 90% confidence intervals for Cₘₚₓ and AUC₀₋ₜ, were within the pre-defined 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 (Metformin Hydrochloride Extended Release Tablets).
Release 1000 mg Tablets) and the reference formulation (Glucophage 1000 mg prolonged release Tablets) under fasting conditions.

**Study 2**
This is an open, randomised, single dose, two-treatment, two-sequence, two-way crossover comparative bioavailability study of Metformin Hydrochloride Extended Release 1000 mg Tablet (test) and Glucophage 1000 mg prolonged release Tablets (reference) in 32 healthy, adult male human subjects under fasting conditions.

Blood samples were collected at 0.00 [pre-dose], 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00, 24.00 and 30.00 hours following drug administration. The washout period was 7 days.

**Results**
Pharmacokinetic parameters for metformin hydrochloride (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

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<tr>
<th>Pharmacokinetic parameter</th>
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<th>Upper 90% CI</th>
<th>Intra-subject CV%</th>
<th>Power</th>
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<tbody>
<tr>
<td>LnC_{max}</td>
<td>98.20</td>
<td>93.48</td>
<td>103.16</td>
<td>11.63</td>
<td>100.00</td>
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<td>Ln\text{AUC}_{0-t}</td>
<td>96.45</td>
<td>89.66</td>
<td>103.76</td>
<td>17.31</td>
<td>99.81</td>
</tr>
</tbody>
</table>

**Conclusion**
The 90% confidence intervals for C_{max} and AUC_{0-t} were within the pre-defined 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 (Metformin Hydrochloride Extended Release 1000 mg Tablets) and the reference formulation (Glucophage 1000 mg prolonged release Tablets) under fasting conditions.

**Study 3**
This is an open, randomised, multiple dose, two-treatment, two-sequence, two-way crossover comparative bioavailability study of Metformin Hydrochloride Extended Release 1000 mg Tablets (test) and Glucophage 1000 mg prolonged release Tablets (reference) in 33 healthy, adult male human subjects under fasting conditions.

Blood samples were collected in pre-labelled K3EDTA vaccutainers at the following time points in each period: - 96.92, -72.92, -48.92, -24.92, -9.2, 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00, 24.00 and 30.00 hours following drug administration. The washout period was 14 days.
Results
Pharmacokinetic parameters for metformin hydrochloride (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

<table>
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<th>Pharmacokinetic parameter</th>
<th>Estimated geometric mean ratio</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
<th>Intra-subject CV%</th>
<th>Power</th>
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</thead>
<tbody>
<tr>
<td>LnCmax,5h</td>
<td>T vs. R</td>
<td>99.31</td>
<td>118.44</td>
<td>21.33</td>
<td>99.29</td>
</tr>
<tr>
<td>LnAUC0-t</td>
<td>T vs. R</td>
<td>96.60</td>
<td>113.21</td>
<td>19.17</td>
<td>99.78</td>
</tr>
</tbody>
</table>

Note: Out of 66 [33 Subjects X 2 periods] possible values, only 27 values were plausible, rest were BLQ and therefore Cmax was not acceptable and hence, not considered for bioequivalence equation.

Conclusion
The 90% confidence intervals for Cmax and AUC0-t were within the pre-defined 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 (Metformin Hydrochloride Extended Release 1000 mg Tablets) and the reference formulation (Glucophage 1000 mg prolonged release Tablets) under fasting conditions.

Study 4
This is an open, randomised, single dose, two-treatment, two-sequence, two period, two-way crossover comparative bioavailability study of Metformin Hydrochloride Extended Release 750 mg Tablets (test) and Glucophage 750 mg prolonged release Tablets (reference) in 22 healthy, adult male human subjects under fed conditions.

Blood samples were collected at 0.00 [pre-dose], 0.50, 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00, 24.00 and 30.00 hours after administration. There was a washout out period of 7 days between the two parts of the studies.

Conclusion
The 90% confidence intervals for Cmax and AUC were within the pre-defined 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 (Metformin Hydrochloride Extended Release 750 mg Tablets) and the reference formulation (Glucophage 750 mg prolonged release Tablets) under fed conditions.

Study 5
This is an open, randomised, single dose, two-treatment, two-sequence, two period, two-way crossover comparative bioavailability study of Metformin Hydrochloride Extended Release 500 mg Tablets (test) and Glucophage 500 mg prolonged release Tablets (reference) in 35 healthy, adult male human subjects under fed conditions.
Blood samples were collected at 0.00 [pre-dose], 0.50, 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 14.00, 16.00, 24.00 and 30.00 hours after administration. There was a washout out period of 7 days between the two parts of the studies.

### Conclusion

The 90% confidence intervals for $C_{\text{max}}$ and $AUC$ were within the pre-defined 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 (Metformin Hydrochloride Extended Release 500 mg Tablet) and the reference formulation (Glucophage 500 mg prolonged release Tablets) under fed conditions.

### IV.3 Pharmacodynamics

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

### IV.4 Clinical efficacy

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

### IV.5 Clinical safety

No new safety data were submitted and none are required.

### IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, 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 Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
### IV.7 Discussion on the clinical aspects

No new clinical data were submitted and none are required for applications of this type.

There are no objections to the approval of these applications from a clinical viewpoint.

The grant of Marketing Authorisations is recommended for these applications.
V  User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Metformin 500 mg immediate release tablets (PL 29831/0133). The bridging report submitted by the applicant is acceptable.

VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with metformin is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.
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 Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets is presented below:
PAR Yaltormin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets

Yaltormin SR 750 mg
Metformin hydrochloride
Prolonged Release Tablets

For oral use

28 prolonged release tablets

Yaltormin SR 750 mg
Metformin hydrochloride
Prolonged Release Tablets
28 prolonged release tablets
Par Yaltomin SR 500 mg, 750 mg and 1000 mg Prolonged Release Tablets

UK/H/5957/001-3/DC
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
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