Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Metformin 500 mg Tablets
Metformin 850 mg Tablets

metformin hydrochloride

PL 43870/0051-0052

Medley Pharma Limited

LAY SUMMARY

Metformin 500 & 850 mg Tablets
metformin hydrochloride

This is a summary of the Public Assessment Report (PAR) for Metformin 500 & 850 mg Tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Metformin Tablets in this lay summary for ease of reading.

For practical information about using Metformin Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Metformin Tablets and what are they used for?
These applications are the same as Metformin 500 & 850 mg Tablets (PL 43870/0004-0005) which are already authorised.

The Company responsible for Metformin 500 & 850 mg Tablets has agreed that its scientific data can be used as the basis for the grant of an identical licence/licences for Metformin Tablets.

Metformin Tablets are used in the treatment of certain patients who are not taking insulin but have diabetes. This form of diabetes is known as Type 2 or 'non-insulin dependent diabetes.
Adults can take Metformin on its own or together with other medicines to treat diabetes (medicines taken by mouth or insulin).
Children 10 years and over and adolescents can take Metformin on its own or together with insulin.

How do Metformin Tablets work?
Metformin contains the active metformin hydrochloride. It belongs to a group of medicines called biguanides. Metformin works by lowering the amount of sugar in the blood. This medicine is given if diet and exercise alone has not been able to control a patients' blood sugar levels.

How are Metformin Tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is oral (by mouth).

Metformin cannot replace the benefits of a healthy lifestyle. The patient should continue to follow any advice about diet that their doctor has given them and get some regular exercise.

Recommended dose
Children 10 years and over and adolescents usually start with 500 mg or 850 mg Metformin once a day. The maximum daily dose is 2000 mg taken as 2 or 3 divided doses. Treatment of children between 10 and 12 years of age is only recommended on specific advice from their doctor, as experience in this age group is limited

Adults usually start with 500 mg or 850 mg Metformin two or three times a day. The maximum daily dose is 3000 mg taken as 3 divided doses.

If the patient has reduced kidney function, their doctor may prescribe a lower dose.
If the patient takes insulin too, their doctor will tell them how to start Metformin.

Monitoring
• The patient's doctor will perform regular blood glucose tests and will adapt their dose of Metformin Tablets to their blood glucose levels. The patient should make sure that they talk to their doctor regularly. This is particularly important for children and adolescents or if they are an older person.
• The patient's doctor will also check at least once a year how well their kidneys work. The patient may need more frequent checks if they are an older person or if their kidneys are not working normally.

How to take Metformin Tablets
Metformin Tablets should be taken with or after a meal. This will avoid having side effects affecting the patients' digestion.

Do not crush or chew the tablets. Swallow each tablet with a glass of water.
• If the patient takes one dose a day, they should take it in the morning (breakfast).
• If the patient takes two divided doses a day, they should take them in the morning (breakfast) and evening (dinner).
• If the patient takes three divided doses a day, they should take them in the morning (breakfast), at noon (lunch) and in the evening (dinner).

If, after some time, the patient thinks that the effect of Metformin Tablets is too strong or too weak, they should talk to their doctor or pharmacist.

For further information on how Metformin Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Metformin Tablets have been shown in studies?
Metformin Tablets are considered identical to the previously authorised products with the same benefits and risks. No new studies have been provided for Metformin Tablets, however, reference is made to the studies for Metformin 500 & 850 mg Tablets.

What are the possible side effects of Metformin Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card

scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Metformin Tablets are considered to be identical to the previously authorised products with the same benefits and risks.

Why were Metformin Tablets approved?
The MHRA decided that the benefits of Metformin Tablets are greater than the risks and recommended that these medicines are approved for use.

What measures are being taken to ensure the safe and effective use of Metformin Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Metformin Tablets The RMP details the important risks of Metformin Tablets, how these risks can be minimised, any uncertainties about Metformin Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Metformin Tablets:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to metformin or any of its excipients • Vitamin B12 decrease/deficiency • Lactic acidosis • Hepatic insufficiency • Use of metformin before elective surgery • Use in patients with renal impairment • Concomitant use with iodinated contrast media
Important potential risks	• Concomitant use with diuretics • Concomitant use with antihypertensive therapy
Missing information	• Use in children inferior to 10 years

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Metformin Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Metformin Tablets
Marketing Authorisations were granted in the UK on 24 September 2024.

The full PAR for Metformin Tablets follows this summary.
This summary was last updated in November 2024.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Metformin 500 & 850 mg Tablets (PL 43870/0051-0052) could be approved.

The products are approved for the following indications:

Non-insulin-dependent diabetes (NIDDM, type II) and, in particular, in obese patients, when adequate dietary treatment and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin 500 mg Tablets and Metformin 850 mg Tablets may be used as monotherapy or in combination with other oral anti-diabetic agents or with insulin.
- In children from 10 years of age and adolescents, Metformin 500 mg Tablets and Metformin 850 mg Tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with Metformin Tablets as first-line therapy after diet failure.

The name of the active substance is Metformin Hydrochloride.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia.

Metformin reduces basal hyperinsulinemia, and in combination with insulin, reduces insulin requirement. Metformin exerts its anti hyperglycaemic effect via multiple mechanisms: Metformin reduces hepatic glucose production. Metformin facilitates peripheral glucose uptake and utilization, in part by increasing insulin action.

Metformin alters glucose turnover in the gut: Uptake from circulation is increased and absorption from food is decreased. Additional mechanisms attributed to the gut include an increase in release of glucagon-like peptide 1 (GLP-1) and a decrease of bile acid resorption. Metformin alters the gut microbiome. Metformin can improve the lipid profile in hyperlipidemic individuals.

These are national abridged applications approved under Regulation 56 of The Human Medicines Regulation 2012, as amended (previously Article 10c of Directive 2001/83/EC, as amended) as informed consent applications. The applications cross-refer to the reference products Metformin 500 & 850 mg Tablets (PL 43870/0004-0005).

No new non-clinical or clinical data have been supplied and none are required for these informed consent applications.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). As the applications are for identical versions of already authorised products, no increase in environmental exposure is anticipated and no ERA is required.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the UK on 24 September 2024.

II. EXPERT REPORT

The applicant cross-refers to the data for Metformin 500 & 850 mg Tablets (Medley Pharma Limited), to which these applications are claimed to be identical. This is acceptable.

III. ASSESSOR'S COMMENTS ON THE PRODUCT INFORMATION

Summaries of Product Characteristics (SmPCs)

The SmPCs are in line with that/those for Metformin 500 & 850 mg Tablets, dated 03/2024.

PATIENT INFORMATION LEAFLET

A leaflet text and mock-up has been provided which has been aligned with that for Metformin 500 & 850 mg Tablets, dated for 07/2023.

LABEL

Label text and mock-ups have been provided.

IV. QUALITY ASPECTS

IV.1 Drug Substance

Drug substance specifications

The sources of the active substance are in line with the cross-reference products. The proposed drug substance specification is consistent with the details registered for the cross-reference products.

IV.2. Drug Product

Name

The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

Metformin 500mg Tablets are to be available in:

PVC/Aluminium in pack sizes of 28 and 84 Tablets.
White Securitainer (LDPE), with tamper-proof closure (HDPE) and a desiccant in pack sizes of 500 and 1000 tablets.

Metformin 850mg Tablets are to be available in:

PVC/Aluminium in pack sizes of 56 Tablets.
Securitainer (HDPE container with polypropylene screw cap with wad having induction sealing liner) in pack sizes of 300 and 600 tablets.

The appearance of the products is identical to that of the cross-reference products.

The proposed shelf life of the product is 3 years with no special storage conditions.

The proposed packaging, shelf life and storage conditions are consistent with the details registered for the reference product.

Legal status
Prescription only medicine (POM).

Manufacturers
The proposed manufacturing sites are consistent with the details registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative compositions
The composition of the proposed products is consistent with the details registered for the cross-reference products.

Manufacturing process & control of critical steps
The proposed manufacturing processes and process controls are consistent with the details registered for the reference products and the maximum batch size is stated.

Finished product release/shelf life specifications
The finished product specifications at release and shelf-life are in line with the details registered for the cross-reference products.

TSE Compliance
No excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

V. NON-CLINICAL ASPECTS

As these applications are submitted under Regulation 56 of The Human Medicines Regulation 2012, as amended, (as informed consent applications) no new non-clinical data have been supplied and none are required.

VI. CLINICAL ASPECTS

As these applications are submitted under Regulation 56 of The Human Medicines Regulation 2012, as amended, (as informed consent applications) no new clinical data have been supplied and none are required.

VII. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

VIII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

IX. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products. The benefit/risk balance is, therefore, considered to be the same as for the cross-reference products and positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**