

Metformin Hydrochloride 500 mg/5 ml Oral Solution

(Metformin hydrochloride)

UK Licence No: PL 04917/0094

UKPAR

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LAY SUMMARY

Metformin Hydrochloride 500 mg/5 ml Oral Solution (Metformin Hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Metformin Hydrochloride 500 mg/5 ml Oral Solution (PL 04917/0094). It explains how Metformin Hydrochloride 500 mg/5 ml Oral Solution was assessed and its authorisation was recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Metformin Hydrochloride 500 mg/5 ml Oral Solution.

For practical information about using Metformin Hydrochloride 500 mg/5 ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Metformin Hydrochloride 500 mg/5 ml Oral Solution and what is it used for?

Metformin Hydrochloride 500 mg/5 ml Oral Solution is a 'generic medicine'. This means that Metformin Hydrochloride 500 mg/5 ml Oral Solution contains the same active substance as, and is similar to a 'reference medicine' already authorised in the UK called Glucophage 500 mg powder for oral solution in sachets (Merck Serono Limited; PL 11648/0088).

Metformin Oral Solution is used to treat patients with type 2 diabetes (also called "non-insulin dependent diabetes") when diet and exercise alone have not been enough to control the blood glucose levels. It is used particularly in overweight patients.

How is Metformin Hydrochloride 500 mg/5 ml Oral Solution used?

This medicine can only be obtained on prescription from the doctor. Metformin Hydrochloride 500 mg/5 ml Oral Solution is taken by mouth with or after a meal. This will help to avoid any side effects affecting the digestion.

The recommended dose is

Adults

- The usual starting dose of Metformin Oral Solution is 5 ml (500 mg) or 8.5 ml (850 mg) two or three times a day
- The maximum daily dose is 30 ml (3000 mg) taken as 3 divided doses.

Use in Children 10 years and over and adolescents

- The usual starting dose of Metformin Oral Solution is 5 ml (500 mg) or 8.5 ml (850 mg) once a day
- The maximum daily dose is 20 ml (2000 mg) taken as two or three divided doses
- Treatment of children between 10 and 12 years of age is only recommended on specific advice from a doctor, as experience in this age group is limited.

A doctor will perform regular blood glucose tests and will adapt the dose of Metformin Oral Solution to the blood glucose levels. The patient should talk to the doctor regularly. This is particularly important for children and adolescents or if the patient is an older person.

How does Metformin Hydrochloride 500 mg/5 ml Oral Solution work?

Metformin Hydrochloride is a type of antidiabetic medicine known as a biguanide. It works in a number of ways to decrease the amount of sugar in the blood of people with type 2 diabetes.

Firstly, it reduces the amount of sugar produced by cells in the liver. Secondly, it increases the sensitivity of muscle cells to insulin. This enables the cells to remove sugar from the blood more effectively. Finally, it delays absorption of sugar from the intestines into the bloodstream after eating.

How has Metformin Hydrochloride 500 mg/5 ml Oral Solution been studied?

The product is an oral solution; the applicant has not performed any clinical trials. No additional studies were needed as Metformin Hydrochloride 500 mg/5 ml Oral Solution is a generic medicine that is given orally and contains the same active substance as the reference medicine, Glucophage 500 mg powder for oral solution in sachets (Merck Serono Limited; PL 11648/0088).

What are the benefits and risks of Metformin Hydrochloride 500 mg/5 ml Oral Solution?

As Metformin Hydrochloride 500 mg/5 ml Oral Solution is a generic medicinal product of Glucophage 500 mg powder for oral solution in sachets (Merck Serono Limited), its benefits and risks are taken as being the same as those for the reference product.

Why is Metformin Hydrochloride 500 mg/5 ml Oral Solution approved?

As no new or unexpected safety concerns arose from this application, it was concluded that the benefits of Metformin Hydrochloride 500 mg/5 ml Oral Solution outweigh the risks; therefore the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Metformin Hydrochloride 500 mg/5 ml Oral Solution?

A risk management plan has been developed to ensure that Metformin Hydrochloride 500 mg/5 ml Oral Solution 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 Metformin Hydrochloride 500 mg/5 ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Metformin Hydrochloride 500 mg/5 ml Oral Solution

A national Marketing Authorisation for Metformin Hydrochloride 500 mg/5 ml Oral Solution was granted in the UK on 17th January 2014.

The full PAR for Metformin Hydrochloride 500 mg/5 ml Oral Solution follows this summary.

For more information about treatment with Metformin Hydrochloride 500 mg/5 ml Oral Solution, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2014.

Metformin Hydrochloride 500 mg/5 ml Oral Solution

PL 04917/0094

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Metformin Hydrochloride 500 mg/5 ml Oral Solution (PL 04917/0094) on 17th January 2014. This product is a prescription-only medicine (POM). Metformin Hydrochloride 500 mg/5 ml Oral Solution is used in the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Metformin Hydrochloride Oral Solution 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 Hydrochloride Oral Solution 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 as first-line therapy after diet failure.

This application was submitted as a national abridged application according to Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross referred to Glucophage 500 mg powder for oral solution in sachets which was originally granted to Lipha Pharmaceuticals Limited (PL 03759/0252) on 19th November 2008. This reference licence then underwent a Change of Ownership (CoA) procedure to Merck Serono Limited (PL 11648/0088), the current Marketing Authorisation, on 1st April 2010.

The active substance metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin may act via 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation and
3. Delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

A pharmacovigilance system and Risk Management Plan have been provided with this application and are satisfactory.

PHARMACEUTICAL ASSESSMENT

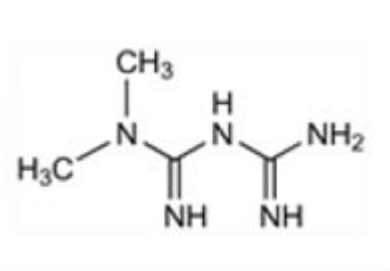
DRUG SUBSTANCE

Nomenclature

rINN: Metformin hydrochloride

Chemical Names: 1,1 Dimethylbiguanide Hydrochloride

Structure:



Molecular Formula: $C_4H_{11}N_5$, HCl

Molecular Weight: 165.6 g/mol

Solubility: Freely soluble in water.

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 a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients liquid maltitol (E965), glycerol (E422), saccharin sodium (E954), propylene glycol (E1520), propyl parahydroxybenzoate (E216), methyl parahydroxybenzoate (E218), sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate (E339), peppermint flavour (contains ethanol), peach flavour (contains propylene glycol and ethanol), hydrochloric acid and purified water.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of peppermint flavour and peach flavour which comply with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that none of the excipients are of animal or human origin.

Pharmaceutical development

The objective of the development programme was to formulate robust, stable, oral solution containing metformin hydrochloride of which could be considered generic medicinal product of Glucophage 500 mg powder for oral solution in sachets (Merck Serono Ltd).

Comparable impurity profiles are provided for this product versus the originator product.

Manufacture

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 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 post approval.

Finished product specification

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

Container Closure System

The product is supplied in an amber (Type III) clear glass bottle with tamper evident, child resistant polypropylene closure and LDPE (low density polyethylene) liner. Each carton contains one bottle and a 10 ml graduated oral syringe (polypropylene, HDPE) with a syringe adaptor (LDPE). The pack sizes are 100 ml and 150 ml.

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, shelf-lives of 12 months for unopened bottle and 60 days once opened with a storage condition "Do not store above 25°C" have been set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are pharmaceutically satisfactory.

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.

Marketing Authorisation Application (MAA) Form

The MAA form is pharmaceutically satisfactory.

Expert Report/Quality Overall Summary

The quality overall summary is 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 this product from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacokinetics

As per guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), a bioequivalence study is not required if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution. As the reference product is considered to be an oral solution at the time of administration, this criterion is deemed fulfilled. Bioequivalence studies may be waived if the excipients contained in the product do not affect gastrointestinal transit, absorption, solubility or *in-vivo* stability of the active substance. These criteria are fulfilled. Therefore, no biostudies are provided by the applicant and none are required.

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 for applications of this type.

Clinical safety

Metformin hydrochloride has an acceptable adverse event profile. No new safety data were supplied or required for this generic application. Metformin hydrochloride has a well-established side-effect profile and is generally well-tolerated.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPC, PIL and labelling are satisfactory from a clinical perspective and consistent with those for the reference product.

Clinical Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form

The MAA form is satisfactory from a clinical perspective.

Clinical Conclusion

There are no objections to the approval of this product from a clinical point of view.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Metformin Hydrochloride 500 mg/5 ml Oral Solution 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 this type.

CLINICAL

No new efficacy data were submitted and none are required for applications of this type. As the safety profile of Metformin hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

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

Metformin Hydrochloride 500 mg/5 ml Oral Solution**PL 04917/0094****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation application on 25 th July 2012
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 10 th August 2012.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 18 th November 2012, 11 th July 2013, 18 th October 2013, 3 rd December 2013 and to the clinical dossier on 4 th October 2012
4	The applicant responded to the MHRA's requests, providing further information to the quality section on 19 th April 2013, 18 th October 2013, 4 th November 2013 and 9 th December 2013 and on the clinical dossier 19 th April 2013
5	The application was determined on 17 th January 2014


SUMMARY OF PRODUCT CHARACTERISTICS

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

PATIENT INFORMATION LEAFLET

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

LABELLING

<p>Metformin Hydrochloride 500 mg/5 ml Oral Solution</p> <p>100 ml</p>  <p>PINEWOOD HEALTHCARE Clonmel, Ireland.</p>	<p>Oral use. Read the package leaflet before use. Each 5 ml of solution contains 500 mg of metformin hydrochloride. Also contains E216, E218, E965, sodium and ethanol. See leaflet for further information. Do not store above 25°C. Discard 60 days after first opening. Date opened: <input type="text"/></p>	
	<p>Keep out of sight and reach of children.</p> <p>Marketing Authorisation Holder: Pinewood Laboratories Ltd., Ballymacarbry, Clonmel, Co. Tipperary, Ireland. PL Number: PL 04917/0094</p>	<p>BN</p> <p>EXP</p> <p>23LL04314PW</p>

<p>Metformin Hydrochloride 500 mg/5 ml Oral Solution</p> <p>150 ml</p>  <p>PINEWOOD HEALTHCARE Clonmel, Ireland.</p>	<p>Oral use. Read the package leaflet before use. Each 5 ml of solution contains 500 mg of metformin hydrochloride. Also contains E216, E218, E965, sodium and ethanol. See leaflet for further information. Do not store above 25°C. Discard 60 days after first opening. Date opened: <input type="text"/></p>	
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