Metformin Hydrochloride 100mg/ml Oral Solution

PL 00289/1416

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Metformin Hydrochloride 100mg/ml Oral Solution (Product Licence number: PL 00289/1416) to Teva UK Limited on 17 August 2011.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use. If you have diabetes your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Metformin helps to lower your blood glucose to as normal a level as possible. If you are an overweight adult, taking metformin over a long period of time also helps to lower the risk of complications associated with diabetes. Metformin is associated with either a stable body weight or modest weight loss.

Metformin 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 your blood glucose levels. It is used particularly in overweight patients. Adults can take metformin on its own or together with other medicines to treat diabetes. Children aged 10 years and over and adolescents can take metformin on its own or together with insulin.

Metformin Hydrochloride 100mg/ml Oral Solution raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
METFORMIN HYDROCHLORIDE 100MG/ML ORAL SOLUTION

PL 00289/1416

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Metformin Hydrochloride 100mg/ml Oral Solution (PL 00289/1416) to Teva UK Limited on 17 August 2011. This medicine is only available on prescription.

Metformin Hydrochloride 100mg/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 the product 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 the product 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 (see section 5.1).

This application is submitted under Article 10.3 of Directive 2001/83/EC, as amended (a hybrid application), as the proposed product is in a different pharmaceutical form to the reference product. The reference product is Glucophage 500 mg film-coated tablets by Merck Sante SAS, registered in France since 19 November 1959. The reference product has, therefore, been authorised in the EEA for at least 10 years and the legal basis of this application is acceptable. The UK reference product is Glucophage 500 mg powder for oral solution in sachets (PL 11648/0088) first licensed in the UK on 19 November 2008 and currently licensed to MERCK SERONO LIMITED.

Assurance has been provided that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

No new preclinical studies were conducted, which is acceptable given that the application refers to an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application refers to an originator product that has been licensed for over 10 years.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: METFORMIN HYDROCHLORIDE

INN: Metformin hydrochloride
Chemical names: 1,1-Dimethylbiguanide monohydrochloride
CAS number: 1115-70-4
Structure:

![Structure of Metformin Hydrochloride]

Molecular formula: C₄H₁₁N₅
Relative molecular mass: 165.6g/mol

General properties
A white or almost white crystalline substance, freely soluble in water, slightly soluble in alcohol, and practically insoluble in acetone and methylene chloride. The melting point is 222.0-226.0°C. There are two polymorphs, both crystalline and with different melting ranges.

Manufacture and control
All aspects of the manufacture and control of the drug substance are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of this drug substance for inclusion in this medicinal product.

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

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

DRUG PRODUCT: METFORMIN HYDROCHLORIDE 100MG/ML ORAL SOLUTION

Excipients
Metformin Hydrochloride 100mg/ml Oral Solution contains the pharmaceutical excipients propylene glycol (E1520), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), orange flavour 10401-7, glycerol (E422), disodium phosphate dihydrate (E339), sodium dihydrogen phosphate dihydrate (E339), saccharin sodium monohydrate (E954) and purified water.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of orange flavour which is controlled by a suitable in-house
specification; in the absence of a European Pharmacopoeia monograph for this excipient this is acceptable. Satisfactory Certificates of Analysis have been provided for all excipients.

All excipients are manufactured by chemical synthesis or are of plant origin and declarations of compliance with BSE/TSE Guidelines have been presented by the manufacturers of each excipient.

**Pharmaceutical development**
The objective of the development programme was to develop a formulation similar to the reference product and to achieve pharmaceutical equivalence in terms of physicochemical properties and dosage form performance. A satisfactory account of the pharmaceutical development has been provided.

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

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

**Container closure system**
The solution comes in 100 ml or 150 ml amber glass bottles with white, plastic, child-resistant polypropylene closures. The bottles come with a plastic (LDPE/PS) pipette with a luer tip (5 ml dose volume graduated every 0.5 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 21 months for product stored in unopened bottles and of 30 days once the bottle has first been opened have been set. These are satisfactory when the storage precaution ‘Do not store above 30°C’ is applied.

**Expert report**
A satisfactory expert report is provided from an appropriately qualified author.

**Product literature**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along 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 it contains.

**Pharmaceutical conclusion**

It is recommended that a Marketing Authorisation is granted for this application.
**PRECLINICAL ASSESSMENT**

As the pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride are well-known, no further preclinical studies are required and none have been provided.

The applicant’s preclinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Submission of an environmental risk assessment is not required with this application.

There are no objections to the approval of this product from a preclinical viewpoint.
INTRODUCTION
Metformin 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 also reduces total cholesterol, LDL cholesterol and triglyceride levels.

INDICATIONS
The applicant proposes the following indications for this product:

“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 (see section 5.1).”

These indications are appropriate for this product.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant proposes the following posology for this product:

Adults:

Monotherapy and combination with other oral antidiabetic agents:

• The usual starting dose is 500mg (5ml) or 850 mg (8.5 ml) metformin hydrochloride 2 or 3 times daily given during or after meals.

• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 3000mg (30ml) daily, taken as 3 divided doses.

• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500mg (5ml) or 850 mg (8.5 ml) 2-3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.
Elderly:
Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Children and adolescents:
*Monotherapy and combination with insulin*

- Metformin Hydrochloride Oral Solution can be used in children from 10 years of age and adolescents.

- The usual starting dose is 500mg (5ml) or 850mg (8.5ml) once daily, given during meals or after meals.

- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 2000mg (20ml) daily, taken as 2 or 3 divided doses.

The required volume for each dose can be achieved with the dosing pipette.”

This posology is appropriate for this product.

**PHARMACOKINETIC STUDIES**

The Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1) states that "Bioequivalence studies may be waived if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution”.

The absence of a bioequivalence study is justified on the following basis:

1. Metformin Hydrochloride 100mg/ml Oral Solution contains the same concentration of drug substance as the marketed product Metsol 500 mg/5 ml oral solution (Orbis, UK), the formulation does not contain excipients liable to affect gastrointestinal transit, absorption or in vivo stability of the active substance. Comparisons of the in vitro performance of the proposed product and the UK reference product show that they are equivalent.

2. Metformin Hydrochloride 100mg/ml Oral Solution is equivalent to another metformin oral solution of the same strength marketed in the United Kingdom (Metsol 500 mg/5 ml oral solution) and also to the UK reference product Glucophage 500 mg powder for oral solution in sachets when diluted in qs 150 ml water. Oral metformin dosage forms are described as bioequivalent in the literature and eligible for biowaiver.

This justification is satisfactory and absence of a bioequivalence study is acceptable.

**PHARMACODYNAMIC STUDIES**

The pharmacodynamic characteristics of the drug substance have been well-studied in the past. There would be no particular concerns for this medicinal product. No new data have been submitted and none are required.
PRODUCT LITERATURE
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

PHARMACOVIGILANCE SYSTEM
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 has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

RISK MANAGEMENT PLAN
The applicant has not submitted an RMP, nor is one needed for an application of this kind.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician. It refers to nine publications up to the year 2009 and is a suitable summary of the clinical aspects of the dossier.

BENEFIT-RISK ASSESSMENT
The application contains an adequate review of published clinical data. The product is approvable in the proposed indication in line with the reference product.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Metformin Hydrochloride 100mg/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.

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

EFFICACY
The efficacy of metformin hydrochloride is well established. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from this application.

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

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with metformin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be acceptable. A Marketing Authorisation should be granted.
METFORMIN HYDROCHLORIDE 100MG/ML ORAL SOLUTION

PL 00289/1416

**STEPS TAKEN FOR ASSESSMENT**

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<td>The MHRA received the Marketing Authorisation application on 23 December 2009</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 15 January 2010</td>
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<td>8</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 13 April 2011</td>
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<td>The application was determined on 17 August 2011</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Metformin Hydrochloride 100mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml of solution contains 100 mg of metformin hydrochloride
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Oral Solution
Clear, homogenous oral solution with a characteristic smell of orange.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
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 (see section 5.1).

4.2 Posology and method of administration
Adults:
Monotherapy and combination with other oral antidiabetic agents:
• The usual starting dose is 500mg (5ml) or 850 mg (8.5 ml) metformin hydrochloride 2 or 3 times daily given during or after meals.
• After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 3000mg (30ml) daily, taken as 3 divided doses.
• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

Combination with insulin:
Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500mg (5ml) or 850 mg (8.5 ml) 2-3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly:
Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

**Children and adolescents:**

**Monotherapy and combination with insulin**

- Metformin Hydrochloride Oral Solution can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500mg (5ml) or 850mg (8.5ml) once daily, given during meals or after meals.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 2000mg (20ml) daily, taken as 2 or 3 divided doses.

The required volume for each dose can be achieved with the dosing pipette.

**4.3 Contraindications**

- Hypersensitivity to metformin hydrochloride or any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60ml/min).
- Acute conditions with the potential to alter renal function such as:
  - dehydration
  - severe infection
  - shock
- Acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure
  - recent myocardial infarction
  - shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism

**4.4 Special warnings and precautions for use**

**Lactic acidosis**

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

**Diagnosis:**

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia. This can be followed by acidotic dyspnoea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient should be hospitalised immediately (see section 4.9).

**Renal function**
As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) should be determined before initiating treatment and regularly thereafter:

• at least annually in patients with normal renal function.
• at least two to four times a year in patients with creatinine clearance level at the lower limit of normal and in elderly subjects.

Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy, diuretic therapy or when starting therapy with a non-steroidal anti-inflammatory drug (NSAID).

**Administration of iodinated contrast media**
The intravascular administration of iodinated contrast media in radiologic studies can lead to renal failure. This may induce metformin accumulation and may expose to lactic acidosis. Metformin must be discontinued prior to, or at the time of the test and not re instituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

**Surgery**
Metformin must be discontinued 48 hours before elective surgery under general spinal or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

**Children and adolescents**
The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated.

No effect of metformin on growth and puberty has been detected during controlled clinical studies of one year duration but no long term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children is recommended.

**Children aged between 10 and 12 years:**
Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

**Other precautions**
• All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
• The usual laboratory tests for diabetes monitoring should be performed regularly.
• Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (*e.g.* sulphonylureas or meglitinides).

**Excipient warnings**
This product contains:
• Parahydroxybenzoates. These may cause allergic reactions (possibly delayed).
4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Alcohol
Acute alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting or malnutrition and hepatic insufficiency.
Avoid consumption of alcohol and alcohol-containing medicinal products.

Iodinated contrast media
Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.
Metformin must be discontinued prior to, or at the time of the test and not be reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be normal (see section 4.4).

Combinations requiring precautions for use
- Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.
- Diuretics, especially loop diuretics: They may increase the risk of lactic acidosis due to their potential to decrease renal function

4.6 Fertility, Pregnancy and lactation

Pregnancy
Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.
A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or post-natal development (see section 5.3).
When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Lactation
Metformin is excreted into human breast milk. No adverse effects were observed in breast-fed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taken into account the benefit of breast-feeding and the potential risk to adverse effects on the child.

Fertility
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.
4.7 **Effects on ability to drive and use machines**

Metformin Hydrochloride Oral Solution monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin, meglitinides).

4.8 **Undesirable effects**

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

**Metabolism and nutrition disorders:**

*Very rare*: Lactic acidosis (see section 4.4).

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloplastic anaemia.

**Nervous system disorders:**

*Common:* Taste disturbance

**Gastrointestinal disorders:**

*Very common:* Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

**Hepatobiliary disorders:**

*Very rare:* Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

**Skin and subcutaneous tissue disorders:**

*Very rare:* Skin reactions such as erythema, pruritus, urticaria

**Paediatric population**

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

4.9 **Overdose**

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Blood glucose lowering drugs, Biguanides
ATC Code: A10B A02
Metformin 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
(3) and 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) known to date.
In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.
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.

Clinical efficacy:
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes.
Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:
• a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034.
• a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;
• a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);
• a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01)
Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.
In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.
Paediatric population
Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption:
After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C$_{\text{max}}$) is reached in approximately 2.5 hours (t$_{\text{max}}$). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C$_{\text{max}}$) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin tablets. Following oral administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution:
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (V$_d$) ranged between 63-276 L.

Metabolism:
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Paediatric population:
Single dose study: After single doses of metformin hydrochloride 500 mg, paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C$_{\text{max}}$) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.
5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- propylene glycol (E1520)
- methyl parahydroxybenzoate (E218)
- propyl parahydroxybenzoate (E216)
- orange flavour 10401-71
- glycerol (E422)
- disodium phosphate dihydrate (E339)
- sodium dihydrogen phosphate dihydrate (E339)
- saccharin sodium monohydrate (E954)
- purified water.

6.2 Incompatibilities
None Known

6.3 Shelf life
Unopened bottles: 21 months
Opened bottles: 30 days

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Amber glass bottles with white plastic child-resistant polypropylene closures.
100 ml and 150 ml of Metformin: 100 mg/ml.

Plastic (LDPE/PS) pipette with luer tip, 5ml dose volume graduated every 0.5ml.

Not all pack sizes maybe marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM
8 MARKETING AUTHORISATION NUMBER(S)
   PL 00289/1416

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
   AUTHORISATION
   17/08/2011

10 DATE OF REVISION OF THE TEXT
    17/08/2011
PATIENT INFORMATION LEAFLET

METFORMIN HYDROCHLORIDE 100mg/ml ORAL SOLUTION

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- If you think it has harmed them, even if their symptoms are the same as yours, if it does not pass on to others.
- If you have any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. What Metformin Hydrochloride 100mg/ml Oral Solution is and what it is used for
2. Before you take Metformin Hydrochloride 100mg/ml Oral Solution
3. How to take Metformin Hydrochloride 100mg/ml Oral Solution
4. Possible side effects
5. How to store Metformin Hydrochloride 100mg/ml Oral Solution
6. Further information

1. WHAT METFORMIN HYDROCHLORIDE 100mg/ml ORAL SOLUTION IS AND WHAT IT IS USED FOR

Metformin Hydrochloride 100mg/ml Oral Solution contains metformin, a medicine to treat diabetes. It belongs to a group of medicines called biguanides.

Insulin is a hormone produced by the pancreas that makes your body take in glucose (sugar) from the blood. Your body uses glucose to produce energy or stores it for future use.

If you have diabetes, your pancreas does not make enough insulin or your body is not able to use properly the insulin it produces. This leads to a high level of glucose in your blood. Metformin helps to lower your blood glucose to as normal a level as possible.

If you are an overweight adult, taking metformin over a long period of time also helps to lower the risk of complications associated with diabetes.

Metformin is associated with either a stable body weight or modest weight loss.

What Metformin Hydrochloride 100mg/ml Oral Solution is used for

Metformin Hydrochloride 100mg/ml Oral Solution is used for Type 2 diabetes patients with 'non-insulin-dependent diabetes', when diet and exercise alone have not taken enough of the blood glucose levels. It is used particularly in overweight patients.

Adults can take Metformin on its own or together with other medicines to treat diabetes (medications taken by mouth or insulin). Children aged 10 years and over and adolescents can take Metformin on its own or together with insulin.

2. BEFORE YOU TAKE METFORMIN HYDROCHLORIDE 100mg/ml ORAL SOLUTION

Do not take Metformin Hydrochloride Oral Solution:

- If you are allergic/disensitized to metformin or any of the other ingredients of this medicine (see ‘What Metformin Hydrochloride 100mg/ml Oral Solution contains’ by Section 6).
- If you have kidney or liver problems.
- If you have uncontrolled diabetes, with e.g. severe hypoglycaemia (low blood glucose), nausea, vomiting, dehydration, rapid weight loss or ketonuria. Ketonuria is a condition in which substances called 'ketone bodies' accumulate in the blood and can lead to diabetic ketoacidosis. Symptoms include stomach pain, fast and deep breathing, sleeplessness or unusual fruity odour of the breath.
- If you have had too much water from your body (dehydration), such as due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see ‘Take special care with Metformin below’).
- If you have a severe infection, such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put your at risk for lactic acidosis (see ‘Take special care with Metformin below’).
- If you are treated for heart failure or have recently had a heart attack, have severe problems with your circulation (such as aneurysa) or have breathing difficulties. This may lead to a lack of oxygen supply to tissues which can put you at risk for lactic acidosis (see ‘Take special care with Metformin below’).
- If you drink a lot of alcohol.
- If any of the above applies to you, talk to your doctor, before you start taking this medicine.

Make sure you ask your doctor before you start taking this medicine:

- You need an examination such as X-ray or scan involving the injection of contrast medicines that contain iodine into your blood stream.
- You need to have major surgery.

You must stop taking Metformin for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment for this time. It is important that you follow your doctor’s instructions precisely.

Take special care with Metformin

Please note the following particular risk of lactic acidosis. Metformin may cause a very rare, but serious complication called lactic acidosis, particularly if your kidneys are not working properly. The risk of lactic acidosis is also increased with uncontrolled diabetes, vomiting, dehydration, alcohol, serious wounds, and difficulty in breathing. This happens to you, you may need hospital treatment, an lactic acidosis may lead to coma. Stop taking Metformin immediately and contact a doctor or the nearest hospital straight way.

Metformin on its own does not cause hypoglycaemia (a blood glucose level which is too low). However, if you take Metformin together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitindine), there is a risk of hypoglycaemia. If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast heart beats, vision disorders or difficulty in concentration, it usually helps to eat or drink something containing sugar.

Taking other medicines

If you need to have an injection of contrast medicines that contain iodine into your bloodstream, for example for an examination such as X-ray or scan, you must stop taking Metformin for a certain period of time before and after the examination (see ‘Make sure you ask your doctor for advice’ above).

Tell your doctor if you take any of the following medicines and Metformin at the same time. You may need more frequent blood glucose tests or your doctor may adjust the dosage of Metformin.

- Diuretics (used to remove water from the body by making more urine)
- Beta-2 agonists such as salbutamol or terbutaline (used to treat asthma)
- Corticosteroids (used to treat a variety of conditions, such as severe inflammation of the skin or in the oesophagus)
- Other medicines used to treat diabetes
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Metformin Hydrochloride Oral Solution with food and drink

You can drink alcohol when you take Metformin. Alcohol may increase the risk of lactic acidosis, especially if you have liver problems or if you are underweight. This also applies to medicines that contain alcohol.

Pregnancy and breast-feeding

During pregnancy, you need insulin to treat your diabetes. Tell your doctor if you are pregnant, you might be or are planning to become pregnant so that he or she may change your treatment.

This medicine is not recommended if you are breast-feeding or if you are planning to breast-feed your baby.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Metformin on its own does not cause hypoglycaemia (a blood glucose level which is too low). This means that it will not affect your ability to drive or use machines. However, take special care if you take Metformin together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitindine). Symptoms of hypoglycaemia include weakness, dizziness, increased sweating, fast heart beats, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms.

Important information about some of the ingredients of Metformin Hydrochloride Oral Solution

This medicine contains:

- Methyland propylparabens. These may cause an allergic reaction (possibly delayed), such as skin rash and difficulty in breathing. If this happens talk to a doctor straight away.

3. HOW TO TAKE METFORMIN HYDROCHLORIDE 100mg/ml ORAL SOLUTION

Always take Metformin Hydrochloride Oral Solution exactly as your doctor has told you.

Check with your doctor or pharmacist if you are not sure.

Metformin alone replaces the benefits of a healthy lifestyle. Continue to follow any advice about diet that your doctor has given you and get some regular exercise.

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**Usual dose.**

Children 10 years and over and adolescents usually start with 500 mg (10 ml) or 800 mg (16 ml) Metformin once a day. The maximum daily dose is 2000 mg (40 ml) taken as two or three divided doses. Treatment of children between 10 and 12 years of age is only recommended on specific advice from your doctor, as experience in this age group is limited.

Adults usually start with 500 mg (5 ml) or 800 mg (8 ml) Metformin two or three times a day. The maximum daily dose is 2000 mg (40 ml) taken as 3 divided doses.

If you take insulin too, your doctor will tell you how to start Metformin.

**Monitoring.**
- Your doctor will perform regular blood glucose tests and will adapt your dose of Metformin to your blood glucose levels. Make sure that you talk to your doctor regularly. This is particularly important for children and adolescents or if you are an older person.
- Your doctor will also check at least once a year if your kidneys work. You may need more frequent checks if you are an older person or if your kidneys are not working normally.

**How to take Metformin.**

Take Metformin with or after a meal. This will avoid you having side effects affecting your appetite.

This solution contains 100 mg of metformin in one 1 ml measurement,
- If you take one dose a day, take it in the morning (breakfast),
- If you take two divided doses a day, take them in the morning (breakfast) and evening (dinner),
- If you take three divided doses a day, take them in the morning (breakfast), at noon (lunch) and in the evening (dinner).

If, after some time, you think that the effect of Metformin is too strong or too weak, talk to your doctor or pharmacist.

If you take more Metformin Hydrochloride Oral Solution than you should:
- If you have taken more Metformin than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are vomiting, feeling sick (nausea), diarrhea, bellyache (abdominal pain) and loss of appetite. These side effects may often happen at the beginning of treatment with Metformin. It helps if you spread the doses over the day and if you take Metformin with or straight after a meal.
- If symptoms continue, stop taking Metformin and talk to your doctor.
- Common side effects (in less than 1 in 10 people):
  - Changes in taste.
  - Very rare side effects (in less than 1 in 10,000 people):
    - Lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly. Symptoms of lactic acidosis are vomiting, feeling sick (nausea) with muscle cramps, a general feeling of not being well with severe tiredness and difficulty in breathing. If this happens to you, you may need immediate hospital treatment, as lactic acidosis may lead to coma. Contact a doctor or the nearest hospital straight away.

**Further Information.**

Keep out of the reach and sight of children. If a child is treated with Metformin, parents and caregivers are advised to oversee how much this medicine is used.

Do not store above 30°C.

Do not use this medicine after the expiry date shown on the label.

**How to Store Metformin Hydrochloride 100 mg/ML Oral Solution.**

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LABELLING

Labels:

Metformin Hydrochloride
100 mg/ml Oral Solution
Oral Use

Each 1 ml of solution contains 100 mg of metformin
hydrochloride. Also contains methanol and water.
Please read the enclosed package leaflet before use. DO NOT
keep out of the reach and sight of children.

Do not store above 30°C. Once opened use within 30 days.
Carton: