

Public Assessment Report

Metformin Tablets 500mg
Metformin Tablets 850mg

Metformin

PL 20117/0020
PL 20117/0021

Morningside Healthcare Limited

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Lay Summary

The MHRA today granted Morningside Healthcare Limited Market Authorisations (licences) for the medicinal products Metformin 500mg Tablets (PL 20117/0020) and Metformin 850mg Tablets (PL20117/0021). These are prescription only medicines (POM) 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. These products contain the active ingredient metformin hydrochloride.

The products were considered the equivalent to the reference product based on two bioequivalence studies and no new safety issues arose as a result of these studies. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Metformin 500mg and 850mg Tablets outweigh the risks hence Marketing Authorisations have been granted.

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Scientific Discussion

INTRODUCTION

Based on the review on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Metformin 500mg Tablets (PL 20117/0020) and Metformin 850mg Tablets (PL 20117/0021) on 25th July 2007. The products are prescription-only medicines. These were National, standard abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to Glucophage 500mg Tablets and 850mg Tablets (Marketing Authorisation Holder: Lipla Pharmaceuticals Limited, UK; PL 03759/0012 for 500 mg, 03759/0013 for 850 mg) which have been authorised in the UK for more than 10 years.

The products contain the active ingredient metformin hydrochloride which is 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. Metformin reduces plasma glucose levels in Type II diabetes by a number of different mechanisms.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

A current Certificate of Suitability was provided for the manufacture of metformin hydrochloride. Metformin is manufactured from only synthetic materials. Satisfactory Certificates of Analysis for batches of the drug substance were provided. Stability results demonstrated the stability of the drug substance under appropriate storage conditions.

DRUG PRODUCT

The tablets are white biconvex, round film-coated tablets and the different strengths can be distinguished by size alone. Appropriate justification for inclusion of each excipient has been provided and all excipients used comply with their respective European Pharmacopoeial monograph.

Name of ingredient
<u>Drug Substance:</u> Metformin hydrochloride
<u>Other Core Ingredients:</u> Sodium starch glycollate
Maize starch
Povidone
Colloidal anhydrous silica
Magnesium Stearate
Weight
<u>Film-coating:</u> Hypromellose
Titanium dioxide
Propylene glycol
Macrogol 6000
Purified Talc

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. 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

Each 500mg pack contains 28 or 84 film-coated tablets. Each 850mg pack contains 56 film-coated tablets. The pack is a PVC/PVC/aluminium blister inside a carton. The specifications are acceptable. It is confirmed that it conforms to EC regulations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “store below 25°C”.

Expert Report

The expert report is written by an appropriately qualified expert and a satisfactory CV was provided.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Glucophage 500mg and 850mg Tablets (Lipha Pharmaceuticals Limited, UK) which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

MEDICAL ASSESSMENT

Indications

The proposed indications for these products are the same as those for Glucophage except that the indication for treatment of children over 10 years of age has been omitted:

"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. Glucophage may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin. A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with metformin as first-line therapy after diet failure."

Scientific evidence

Metformin hydrochloride, a biguanide used in the treatment of NIDDM, is a well established product, outside patent life. No clinical pharmacodynamic, efficacy or safety studies are required. An adequate literature review has been submitted to cover those aspects.

No new pharmacodynamic data are presented and none are required.

Bioequivalence

Two bioequivalence studies were performed, one with 500 mg and one with 850 mg tablets. Both studies were identical in design. The reference drug materials used were Glucophage 500 and 850 mg tablets manufactured by Lipha Pharmaceuticals Ltd.

Study design

24 healthy, adult, male volunteers were recruited to each bioequivalence study, all of whom completed the studies. The mean weights of subjects were 72.4 and 77.1 kg and mean heights were 178.6 and 181.0 cm for the 500 and 850 mg studies, respectively. A single oral dose of each drug was administered with a 7-10 day washout between dosing periods. Subjects were randomised to order of dosing. Single dosing is justifiable based on the known pharmacokinetic characteristics of metformin. The 7-10 day interval is justifiable on the basis of the known plasma half-life of the drug and the absence of analytes in pre-dose samples.

Confirmation has been given by the Quality Assessor that the test drug materials used were considered suitable, in terms of content and sampling.

In each period, subjects were institutionalised from the evening before to 16 hours after dosing and were to return at 24, 36 and 48 hours post-dosing for blood sampling. Subjects were fasted from 10 hours prior to dosing and appropriate restrictions on diet, fluid intake and concomitant medications were maintained.

Blood samples were taken at intervals appropriate to the known pharmacokinetic profile of the drug up to 48 hours after dosing and analysed for metformin

concentrations. The following pharmacokinetic parameters were reported: $AUC_{(0-inf)}$, C_{max} , $AUC_{(0-t)}$, T_{max} , $T_{1/2}$ and K_{el} . Analysis of variance was conducted using period, sequence and treatment as variables. 90% confidence intervals (CI) for the ratio of the geometric means of the log-transformed values were presented and compared to the accepted ranges: 80 - 125% for the AUCs and 70 -143% for C_{max} .

Confirmation has been given by the Quality Assessor considers the drug analysis methods used to be satisfactory.

Results

There were no protocol deviations which were expected to affect study results.

A summary of the results is represented below for log-transformed data:

Table 1: Summary of comparative bioavailability - Metformin 500 mg Tablets

Parameter (units)	Geometric mean for test product (\pm SD)	Geometric mean for reference (\pm SD)	Ratio (%)	90% CI (non-parametric, %)
$\ln C_{max}$ ($\mu\text{g/ml}$)	0.922 ± 0.169	0.921 ± 0.263	102	93.6-112
$\ln AUC_{(0-last)}$ ($\mu\text{g}\cdot\text{h/ml}$)	6.86 ± 1.22	6.69 ± 1.83	104	98.0-111
$\ln AUC_{(0-inf)}$ ($\mu\text{g}\cdot\text{h/ml}$)	6.91 ± 1.22	6.75 ± 1.82	104	97.9-111

Table 2: Summary of comparative bioavailability - Metformin 850 mg Tablets

Parameter (units)	Geometric mean for test product (\pm SD)	Geometric mean for reference (\pm SD)	Ratio (%)	90% CI (non-parametric, %)
$\ln C_{max}$ ($\mu\text{g/ml}$)	1.40 ± 0.290	1.48 ± 0.308	93.5	88.4-100.4
$\ln AUC_{(0-last)}$ ($\mu\text{g}\cdot\text{h/ml}$)	9.53 ± 1.90	10.2 ± 2.30	93.0	87.7-99.0
$\ln AUC_{(0-inf)}$ ($\mu\text{g}\cdot\text{h/ml}$)	9.63 ± 1.92	10.3 ± 2.34	93.1	88.0-99.1

Confirmation has been given by the Quality Assessor that the drug product samples and analytical methods used in these bioequivalence studies are satisfactory.

Discussion

These results show that the confidence intervals for all three pharmacokinetic parameters fall within the prescribed limits (80-125%) for bioequivalence for metformin for both tablet sizes.

This bioequivalence study appears to have been conducted according to the appropriate NfG and to have shown bioequivalence between test and reference products at both tablet strengths. Individual plasma concentration/time curves were inspected and found to be satisfactory, without undue inter-individual variability.

The results of these studies demonstrate the bioequivalence of the products.

Efficacy and Safety

No new efficacy data are presented in this application and none are required.

No formal safety data are presented and none are required.

Summary of Product Characteristics

This is satisfactory

Patient Information Leaflet

This satisfactory

Conclusions

Market authorisations may be granted for these products.

Overall Conclusion and Risk/Benefit Analysis

Quality

The quality aspects of Metformin 500mg and 850mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Pre-Clinical

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

Clinical

Bioequivalence has been demonstrated between the two products and the reference products.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Monotrim tablets.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with metformin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 21 st March 2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 10 th April 2006
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 15 th August 2006, 2 nd February 2007 and 27 th March 2007 and on the medical assessment on 17 th August 2006.
4	The applicant provided further information in regard to the quality assessment on 12 th January 2007, 27 th March 2007 and 16 th May 2007 and on the medical assessment on 20 th July 2007
5	The application was determined on 25 th July 2007.

Steps Taken after Assessment

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin 500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film coated tablet contains;

500mg Metformin Hydrochloride

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

White, circular, convex film-coated tablets

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 film-coated 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 film-coated tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with Metformin as first-line therapy after diet failure (see 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Adults

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is one 500mg tablet 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 is 3 g daily taken as 2-3 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 is given at the usual starting dose of one tablet 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 from 10 years of age and adolescents

Monotherapy and combination with insulin

The usual starting dose is one 500mg or 850mg tablet 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 is 2g daily taken as 2-3 divided doses.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 $\mu\text{mol/L}$ in males and > 110 $\mu\text{mol/L}$ in females).
- Acute conditions with the potential to alter renal function such as:
 - dehydration
 - severe infection
 - shock
 - Intravascular administration of iodinated contrast agents (see 4.4 Warnings and special precautions for use).
- 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
- Lactation

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:

Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/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, serum creatinine levels 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 serum creatinine levels at the upper 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 or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

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 metformin efficacy and safety in children below 12 did not differ from efficacy and safety in older children, 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 never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Alcohol

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition
- hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents (see section 4.4)

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

4.6 Pregnancy and lactation

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development (see also section 5.3)

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7 Effects on ability to drive and use machines

Metformin 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 (sulfonylureas, insulin, repaglinide).

4.8 Undesirable effects

The following undesirable effects 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 $<1/10,000$ and isolated reports.

Metabolism and nutrition disorders

Very rare: 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 megaloblastic anaemia.

Very rare: Lactic acidosis (see 4.4. Special warnings and precautions for use).

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:

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

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

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 doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin 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

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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) 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 (GLUT).

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 ($p=0.01$)

For metformin used as second-line therapy, in combination with a sulfonylurea, benefit regarding clinical outcome has not been shown.

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.

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, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin 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 are non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following 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 decreases 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 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.

Paediatrics:

Single dose study: After single doses of metformin 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 BID for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg BID 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, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

- Sodium starch glycollate (Type A)
- Maize starch
- Povidone K 30
- Colloidal anhydrous silica
- Magnesium stearate

Film-coating

- Methylhydroxypropylcellulose
- Titanium dioxide E171
- Propylene glycol
- Polyethylene glycol 6000
- Purified talc

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister pack of 28 or 84 film-coated tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

115 Narborough Road

Leicester

LE3 OPA

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0020

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

25/07/2007

10 DATE OF REVISION OF THE TEXT

25/07/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metformin 850mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film coated tablet contains;

850mg Metformin Hydrochloride

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

White, circular, convex film-coated tablets

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 film-coated 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 film-coated tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic patients treated with Metformin as first-line therapy after diet failure (see 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Adults

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is one 500mg tablet 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 is 3 g daily taken as 2-3 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 is given at the usual starting dose of one tablet 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 from 10 years of age and adolescents

Monotherapy and combination with insulin

The usual starting dose is one 500mg or 850mg tablet 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 is 2g daily taken as 2-3 divided doses.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (e.g., serum creatinine levels > 135 $\mu\text{mol/L}$ in males and > 110 $\mu\text{mol/L}$ in females).
- Acute conditions with the potential to alter renal function such as:
 - dehydration
 - severe infection
 - shock
 - Intravascular administration of iodinated contrast agents (see 4.4 Warnings and special precautions for use).
- 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
- Lactation

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:

Lactic acidosis is characterised by acidotic dyspnea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/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, serum creatinine levels 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 serum creatinine levels at the upper 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 or diuretic therapy and when starting therapy with an NSAID.

Administration of iodinated contrast agent

As the intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure, metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Surgery

Metformin hydrochloride should be discontinued 48 hours before elective surgery with general anaesthesia and should not usually be resumed earlier than 48 hours afterwards.

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 metformin efficacy and safety in children below 12 did not differ from efficacy and safety in older children, 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 never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or sulfonylureas

4.5 Interaction with other medicinal products and other forms of interaction**Concomitant use not recommended****Alcohol**

Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:

- fasting or malnutrition
- hepatic insufficiency

Avoid consumption of alcohol and alcohol-containing medications.

Iodinated contrast agents (see section 4.4)

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis.

Metformin should be discontinued prior to, or at the time of the test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, adjust the dosage of the antidiabetic drug during therapy with the other drug and upon its discontinuation.

4.6 Pregnancy and lactation

To date, no relevant epidemiological data are available. Animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development (see also section 5.3)

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with metformin but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Metformin is excreted into milk in lactating rats. Similar data are not available in humans and a decision should be made whether to discontinue nursing or to discontinue metformin, taking into account the importance of the compound to the mother.

4.7 Effects on ability to drive and use machines

Metformin 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 (sulfonylureas, insulin, repaglinide).

4.8 Undesirable effects

The following undesirable effects 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 $<1/10,000$ and isolated reports.

Metabolism and nutrition disorders

Very rare: 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.

Very rare: Lactic acidosis (see 4.4. Special warnings and precautions for use).

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:

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

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

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 doses of up to 85g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin 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

ORAL ANTI-DIABETICS

(A10BA02: Gastrointestinal tract and metabolism)

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) 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 (GLUT).

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 ($p=0.01$)

For metformin used as second-line therapy, in combination with a sulfonylurea, benefit regarding clinical outcome has not been shown.

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.

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, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin 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 are non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 4 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following 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 decreases 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 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.

Paediatrics:

Single dose study: After single doses of metformin 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 BID for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg BID 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, toxicity reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

- Sodium starch glycollate (Type A)
- Maize starch
- Povidone K 30
- Colloidal anhydrous silica
- Magnesium stearate

Film-coating

- Methylhydroxypropylcellulose
- Titanium dioxide E171
- Propylene glycol
- Polyethylene glycol 6000
- Purified talc

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister pack of 28 or 84 film-coated tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd

115 Narborough Road

Leicester

LE3 OPA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0020

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

25/07/2007

10 DATE OF REVISION OF THE TEXT

25/07/2007

Labels and Leaflet

PATIENT INFORMATION LEAFLET Metformin 500mg or 850mg Tablets

PLEASE 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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you and should not pass it on to other people. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious or if you notice any side effects not listed on this leaflet, please tell your doctor or pharmacist

In this leaflet:

- | | |
|-------------------------------|---------------------------|
| 1. What Metformin is used for | 4. Possible side effects |
| 2. Before you take Metformin | 5. How to store Metformin |
| 3. How to take Metformin | 6. Further information |

1. WHAT IS METFORMIN AND WHAT IS IT USED FOR?

These white film coated tablets contain either 500mg or 850mg of the active ingredient Metformin Hydrochloride. Metformin is an oral anti-diabetic, which works by reducing the level of sugar in the blood. Metformin Tablets are used for the treatment of diabetes which usually is more common in overweight people and which does not respond to dietary measures and exercise alone. Metformin can be used alone or in combination with other drugs against diabetes, including insulin.

2. BEFORE YOU TAKE METFORMIN

Do not take Metformin

- if you are allergic to any of the ingredients in this medicine?
- if you have fainted or suffered a coma due to your diabetes?
- if you have any problems with your liver or kidneys?
- if you have had a severe fever or you are unwell in any other way?
- if you have a heart disorder or problems with your circulation e.g. frequent cramp in your calves or leg ulcers that do not heal?
- if you are pregnant intending to become pregnant or breast-feeding?
- if you are likely to have surgery or a scan involving the use of X-rays
- if you are on a special diet?
- if you drink alcohol?

Take special care with Metformin

If the patient has kidney failure, blood levels of Metformin can increase, and this can very rarely cause lactic acidosis. Lactic acidosis can result in breathing problems, muscle pains or the loss of consciousness. If not treated this can be very dangerous and so urgent hospital attention is needed. In this case you must contact your doctor immediately or go to the nearest hospital accident and emergency department.

Taking other medicines

Metformin may interact with other medicines, even those that are not prescribed. Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

The effects of Metformin may be altered by:

- Other medicines used to lower blood sugar e.g. insulin
- Angiotensin converting enzyme (ACE) inhibitors e.g. captopril or enalapril
- Beta blockers e.g. propranolol
- Diuretics ("water tablets") e.g. furosemide
- Steroids e.g. cortisone, or prednisolone
- Non-steroidal anti-inflammatory drugs (NSAIDS)

Taking Metformin with food and drink

The tablets should be swallowed whole with a glass of water. Metformin does not interact with food but taking after food can reduce some side effects. **Avoid alcohol while taking Metformin**

Pregnancy and breast-feeding

Do not take Metformin if you are pregnant or breast feeding. Tell your doctor **immediately** if think you are pregnant.

Driving and using machines:

Metformin does not affect your ability to drive vehicles or handle machinery, but if you are also taking other anti-diabetic medicines it is possible that you may feel faint, dizzy or weak. If this happens you should not drive or operate any machinery until you have recovered

3. HOW TO TAKE METFORMIN

Always take Metformin tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

Children from 10 years and adolescent is: one 500mg tablet daily. If the dose needs to be increased then the stronger 850mg tablets may be used, Your doctor may increase the dose to a maximum of 2000mg per day taken in divided doses.

Adults: is 500mg 2 or 3 times daily. If the dose needs to be increased then the stronger 850mg tablets may be used. Your doctor may increase the dose to a maximum of 3000mg per day taken in divided doses.

Your doctor will test your blood glucose and your kidney function at intervals while you are taking Metformin to make sure you are taking the right dose. This is especially important when you start taking other new medicines at the same time as Metformin

If you take more Metformin than you should

Tell your doctor or contact the nearest hospital, taking the medicine or this leaflet with you.

If you forget to take Metformin

As soon as you remember take the missed dose, unless it is nearly time for the next dose.

Never take two doses at the same time.

If you stop taking Metformin

If you stop taking Metformin, tell your doctor as soon as possible, as your diabetes will not be controlled.

If you have any further questions on the use of this product ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines Metformin can cause side effects, although not everybody gets them.

If you develop muscle pains, tingling in the fingers or toes, breathing problems or start to lose consciousness- in this case you must, contact your doctor **immediately** or go to the nearest hospital accident and emergency department. Metformin can rarely cause a condition called "lactic acidosis" which has these symptoms and can be very dangerous so needs urgent hospital attention.

It is **very common** (1 in 10) to have stomach pains or stomach upsets such as nausea, vomiting, diarrhoea, loss of appetite or a metallic taste. **Very rarely** (<1 in 10,000) a rash occurs. These effects usually get better spontaneously and you should continue to take the tablets. If these do not get better after a few days, tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE METFORMIN

Keep all medicines out of the reach and sight of children, preferably in a locked cupboard or medicine cabinet. **Do not take the tablets after the expiry date on the pack.** Do not store the tablets above 25°C.

6. OTHER INFORMATION

The other ingredients in the tablets are sodium starch glycollate, maize starch, povidone, colloidal anhydrous silica, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide (E171), propylene glycol, polyethylene glycol 6000 and purified talc.

Metformin tablets are available in blister packs of 28, 84 (500mg) or 56 (850mg) tablets.

Marketing Authorisation Holder: Morningside Healthcare Ltd, 115 Narborough Road, Leicester, LE3 0PA. UK.

Manufacturer: Micro Labs Ltd, 93 Sipcot Industrial Complex, Hosur, India.

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