Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Metformin 500mg Tablets
Metformin 850mg Tablets

Metformin Hydrochloride

UK/H/885/01-02/MR
UK licence no: PL 20117/0001-2

Morningside Healthcare Limited

LAY SUMMARY

The MHRA has granted Morningside Healthcare Limited Marketing Authorisations (licences) for the medicinal products Metformin Tablets (500mg and 850mg) on 17th April 2007. These are prescription-only medicines for the treatment of diabetes in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate control of sugar in the blood. These products contain the active ingredient metformin hydrochloride.

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.

TABLE OF CONTENTS

Module 1

Product Name	Metformin 500mg Tablets Metformin 850mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Metformin Hydrochloride
Form	Film-Coated Tablets
Strength	500mg and 850mg
MA Holder	Morningside Healthcare Limited, 115 Narborough Road, Leicester, LE3 0PA, UK
Reference Member State (RMS)	UK
CMS	Belgium, Czech Republic, Germany, Denmark, Estonia, Finland, France, Hungary, Italy, Lithuania, Latvia, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia and Slovakia and Spain.
Procedure Number	UK/H/0885/001-2/MR
Timetable	Day 90 – 17th April 2007

Module 2
SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The UK Summaries of Product Characteristics (SPC) for Metformin 500mg and 850mg Tablets are as follows:

1. TRADE NAME OF THE MEDICINAL PRODUCT
Metformin 500mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 film coated tablet contains;
500mg Metformin (as hydrochloride)

For 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 in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic 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 (see 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

Monotherapy and combination with other oral antidiabetic agents

- The usual starting dose is one 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.
- 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: In the absence of data, Metformin should not be used in children.

4.3 Contra-indications
• 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 µmol/L in males and > 110 µmol/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 reinstituted 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.

-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 reinstituted 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

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.

Lactation

Metformin is excreted into milk in lactating rats. Similar data is 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

- Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (>10%) are very common: these occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent these gastrointestinal symptoms, 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.
- Metallic taste (3%) is common.
- Mild erythema has been reported in some hypersensitive individuals The incidence of such effects is regarded as very rare (<0.01%).
- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).
- Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see 4.4 Warnings and special precautions for use).

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.

5.2 Pharmacokinetic Properties

Absorption:

After an oral dose of metformin, Tmax 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 (Cmax) 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 Vd 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.

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.

6.1 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

2 years

6.4 Special Precautions for storage

Store below 25°C

6.5 Nature and Contents of Container

Blister pack of 20, 28, 30, 50, 56, 60, 84, 90,100 and 120 film-coated tablets

6.6 Instructions for use/handling

No special precautions are required

7. MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 20117/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2005

10 DATE OF REVISION OF THE TEXT

15/09/2005

1. TRADE NAME OF THE MEDICINAL PRODUCT

Metformin 850mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film coated tablet contains;
850mg Metformin (as hydrochloride)

For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets
White, circular, convex film-coated tablets

4. CLINICAL PARTICULARS

4.2. Therapeutic indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic 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 (see 5.1 Pharmacodynamic properties).

4.2 Posology and method of administration

-Monotherapy and combination with other oral antidiabetic agents

- The usual starting dose is one 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.
- 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: In the absence of data, Metformin should not be used in children.

4.3 Contra-indications

• 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 µmol/L in males and > 110 µmol/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
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As metformin is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter:
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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.

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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 reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

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

-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:
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Avoid consumption of alcohol and alcohol-containing medications.

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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.

Lactation

Metformin is excreted into milk in lactating rats. Similar data is 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).

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- Mild erythema has been reported in some hypersensitive individuals The incidence of such effects is regarded as very rare (<0.01%).
- A decrease of vitamin B12 absorption with decrease of serum levels has been observed in patients treated long-term with metformin and appears generally to be without clinical significance (<0.01%).
- Lactic acidosis (0.03 cases/1000 patient-years) is very rare (see 4.4 Warnings and special precautions for use).

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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

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(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.

5.2 Pharmacokinetic Properties

Absorption:

After an oral dose of metformin, Tmax 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 (Cmax) 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 Vd 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.

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.

6.1 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

2 years

6.4 Special Precautions for storage

Store below 25°C

6.5 Nature and Contents of Container

Blister pack of 20, 28, 30, 50, 56, 60, 84, 90,100 and 120 film-coated tablets

6.6 Instructions for use/handling

No special precautions are required

7. MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom

8. MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/09/2005

10 DATE OF REVISION OF THE TEXT

15/09/2005

Module 3

Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Metformin Hydrochloride 500 mg film coated tablets
Metformin Hydrochloride 850 mg film coated tablets

Metformin hydrochloride

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 pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. 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 IS METFORMIN AND WHAT IS IT USED FOR

Metformin belongs to a group of drugs called biguanides which are used in the treatment of diabetes. Metformin film coated tablets contain the active ingredient metformin hydrochloride. Each tablet contains either 500 mg or 850 mg of metformin hydrochloride.

Metformin is used for the treatment of Type 2 (non-insulin dependent) diabetes mellitus particularly in overweight patients, where diet and exercise changes alone have not been sufficient to control it. In type 2 diabetes, there is too much sugar (glucose) is in your blood because your pancreas does not produce enough insulin or because it produces insulin that does not work properly.

Adults
Your doctor can prescribe metformin for you to take on its own, or in combination with other oral antidiabetic medicines, or insulin.

Children aged 10 years or above and adolescents
Your doctor can prescribe metformin for you to take on its own, or in combination with insulin.

2. BEFORE YOU TAKE METFORMIN

Do not take Metformin

- if you are you allergic (hypersensitive) to metformin or to any of the ingredients in this medicine.
- if you have had serious complications with your diabetes or other serious conditions which resulted in rapid weight loss, nausea, vomiting or dehydration and you had fainted or suffered a coma due to your diabetes.
- if you have any problems with your liver or kidneys.
- if you are suffering from severe infection or have recently suffered a severe injury.
- if you have been treated for heart problems or have recently had a heart attack or have problems with your circulation (e.g. frequent cramp in your calves or leg ulcers that do not heal) or breathing difficulties.
- if you are pregnant or breast-feeding.
- if you are likely to have surgery or a scan or an X-ray.
- if you drink alcohol.

Take special care with Metformin

If you have diabetes you should have your blood or urine tested for sugar regularly. You should return to your doctor at least once a year to check the function of your kidneys (more often if you are elderly or if you have kidney problems)

If you have kidney failure, blood levels of metformin can increase, which can very rarely cause lactic acidosis. This results in breathing problems, muscle pains or loss of consciousness and if not treated this can be very dangerous so needs urgent hospital attention. In this case you must contact your doctor immediately or go to the nearest hospital accident and emergency department.

If you need to have an X-ray examination tell your doctor that you take metformin as you may need to stop taking it for few days afterwards.

Tell your doctor if surgery is planned. Treatment with metformin should be stopped 2 days before surgery until at least 2 days following surgery.

You should continue your diet during treatment with metformin with an even intake of carbohydrate over the day. If you are overweight continue your energy-restricted diet under medical supervision.

No effect of metformin on growth and puberty has been detected although few children between the age of 10 and 12 years have been studied. Growth and puberty should be carefully monitored in children and adolescents.

Normal kidneys are essential for the treatment with metformin because of the risk of developing lactic acidosis. Tests will be done to check your kidney function at least once a year or more frequently if you are elderly, or when starting treatment for high blood pressure.

Taking metformin alone does not normally cause low blood sugar levels (hypoglycaemia). Taking metformin in combination with medicines called sulphonylureas, insulin or other treatments for diabetes may cause low blood sugar levels with symptoms such as sweating, fainting, dizziness or weakness, so in this case you should take extra care when driving or operating machinery.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.
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.
- Betablockers e.g. propranolol.
- Diuretics (water tablets) e.g. furosemide or NSAID (non-steroidal anti-inflammatory drugs e.g. ibuprofen) you may be at increased risk of kidney problems.
- Glucocorticoids e.g. cortisone, budesonide, beclomethasone or prednisolone.
- Alcohol containing medicines.
- Medicines used in the treatment of asthma such as salbutamol.
- Metformin must not be used at the same time as iodinated contrast media which may be used for medical imaging e.g. X-rays or scans because there is a risk of kidney failure. If you are going to undergo these procedures, you must tell your doctor you are taking Metformin. It is advised to stop taking Metformin for 48 hours before and after the procedure.

Taking Metformin with food and drink

The tablets should be swallowed whole with a glass of water during or after meals. This 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:

Adults: The usual starting dose is one or two 500 mg or 850 mg tablets two or three times a day.. Your doctor may increase the dose to a maximum of 3000 mg per day taken as divided doses.

Elderly: The starting dose will be determined after tests have been carried out on your kidney function.

Children aged 10 years and older and adolescents: Normally the starting dose is one 500 mg tablet daily. If the dose needs to be increased, 850 mg tablets may be used. Your doctor may increase the dose to a maximum of 2000 mg per day taken as 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

Take the missed dose as soon as you remember, but if your next regular dose is less than 2 hours away, skip the regular one.
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 start to lose weight unexpectedly, feel sick with stomach pains, have rapid uncontrolled breathing, or start to lose consciousness, you should stop taking the drug and, contact your doctor **immediately** or go to the nearest hospital accident and emergency department. These can be signs of very rare condition called "lactic acidosis" which can be dangerous and needs urgent hospital attention.

It is **very common** (affecting more than one person in 10) to have stomach pains or stomach upsets such as nausea, vomiting, diarrhoea, loss of appetite or a taste disturbance. **Very rarely** (affecting fewer than one in 10,000) a rash occurs (redness and itching of the skin, hives). 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.

Very rarely:
Liver problems (hepatitis), possibly with jaundice (such yellowing of skin and eyes) which goes away on stopping metformin.
A decrease in vitamin B12 absorption, which can result in anaemia, sore tongue, tingling and numbness.

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 of the reach and sight of children. **Do not take metformin tablets after the expiry date printed on the blister pack and carton.,** The expiry date refers to the last day of that month
Do not store above 25C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Metformin contains

The active substance is Metformin hydrochloride. Each film coated tablet contains 500 mg or 850 mg metformin hydrochloride. The other ingredients in the tablets are sodium starch glycolate (Type A), maize starch, povidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide (E171), propylene glycol, macrogol 6000 and purified talc.

What Metformin looks like and contents of the pack

Metformin 500 mg film coated tablets are white, circular, bi-convex with diameter of 11 mm.

Metformin 850 mg film coated tablets are white, circular, bi-convex with diameter of 13.5 mm.

Metformin tablets are available in blister packs of 20, 28, 30, 50, 56, 60, 84, 90, 100 or 120 tablets(500 mg) and 20, 28, 30, 50, 56, 60, 84, 90, 100 or 120 tablets (850 mg)..

Not all pack sizes may be marketed

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

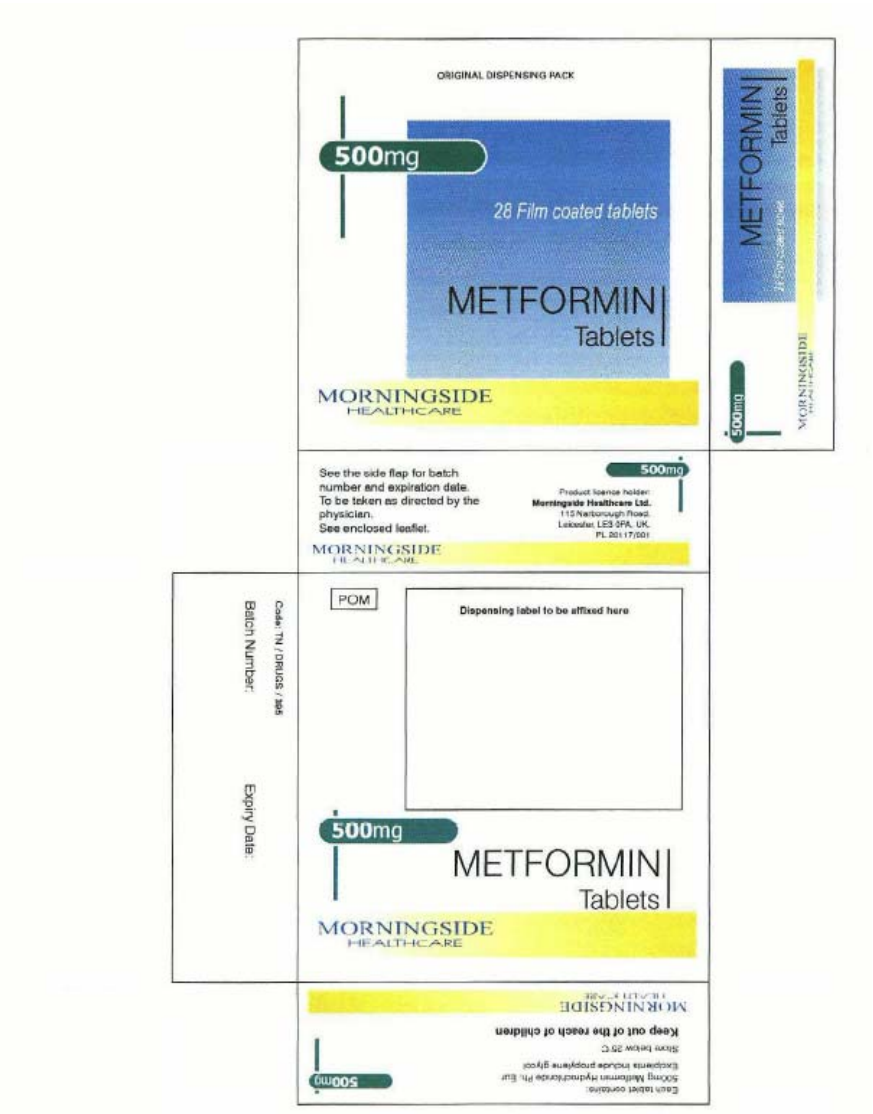
Manufacturer:
Morningside Leicester Ltd
115 Narborough Road
Leicester, UK

This medical product is authorised in the Member States of the EEA under the following names:

Czech Republic	Glumetsan
Estonia	Glumetsan
Ireland	Metformin Hydrochloride Tablets
Latvia	Glumetsan
Lithuania	Glumetsan
Poland	Glumetsan
Portugal	Metformin-Genmed
Slovak Republic	Glumetsan
Spain	Metformin-Aldo-Unión.
United Kingdom	Metformin Hydrochloride Tablets

This leaflet was last updated in September 07

Module 4
Labelling




ORIGINAL DISPENSING PACK
850mg
56 Film coated tablets
METFORMIN
Tablets
MORNINGSIDE
HEALTHCARE
56 Film coated tablets
METFORMIN
Tablets
850mg
MORNINGSIDE
HEALTHCARE
See the side flap for batch number and expiration date.
To be taken as directed by the physician.
See enclosed leaflet.
850mg
Product licence holder:
Morningside Healthcare Ltd.
115 Narborough Road,
Leicester, LE3 0PA, UK.
PL 20117/000
MORNINGSIDE
HEALTHCARE
POM
Dispensing label to be affixed here
Batch Number:
Expiry Date:
850mg
METFORMIN
Tablets
MORNINGSIDE
HEALTHCARE
Each tablet contains:
850mg Metformin Hydrochloride Ph. Eur
Excipients include propylene glycol
Store below 25°C
Keep out of the reach of children
MORNINGSIDE
HEALTHCARE
850mg

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Metformin 500mg Tablets and Metformin 850mg Tablets in the treatment of type 2 diabetes mellitus in adults, could be approved. National marketing authorisations were granted on 15th September 2005.

These are applications made under Article 10.1 of 2001/83 EC, as amended, for Metformin 500mg Tablets and Metformin 850mg Tablets and have been shown to be generic medicinal products of the originator product, Glucophage 500mg Tablets (Marketing Authorisation Holder: Lipha Pharmacetuicals Limited, UK).

The biguanide metformin hydrochloride is an oral antihyperglycaemic agent used in the management of diet-failed non-insulin dependent diabetes mellitus (NIDDM). It is especially used in overweight patients or in those for whom attempts to achieve acceptable control with sulfonylurea therapy and physical activity have failed. Since metformin does not promote weight gain or hypoglycaemia, it is considered as first-line pharmacotherapy in obese patients with NIDDM inadequately controlled by non-pharmacological measures. Metformin appears similarly effective in the pharmacological management of NIDDM in non-obese patients.

Metformin acts by reducing elevated blood glucose levels, predominantly by improving hepatic and peripheral tissues sensitivity to insulin without affecting secretion of this hormone.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Metformin 500mg Tablets Metformin 850mg Tablets
Name(s) of the active substance(s) (INN)	Metformin Hydrochloride
Pharmacotherapeutic classification (ATC code)	Drugs used in diabetes (A10 BA02)
Pharmaceutical form and strength(s)	500mg and 850mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/885/01-02/MR
Reference Member State	United Kingdom
Member States concerned	Belgium, Czech Republic, Germany, Denmark, Estonia, Finland, France, Hungary, Italy, Lithuania, Latvia, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia and Slovakia and Spain.
Marketing Authorisation Number(s)	PL 20117/0001-2
Name and address of the authorisation holder	Morningside Healthcare Limited, 115 Narborough Road, Leicester, LE3 0PA, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

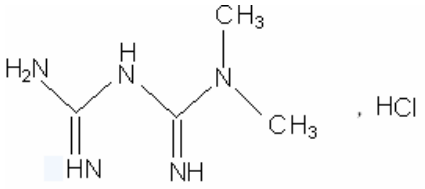
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Metformin hydrochloride

Chemical name: 1-(diaminomethylidene)-3,3-dimethyl-guanidine

Structural formula



Molecular formula: $C_4H_{12}ClN_5$

Molecular weight: 165.6

General Properties

Solubility: Freely soluble in water,

Melting point: 220-222˚C.

Metformin hydrochloride is the subject of a European Pharmacopoeia monograph.

A Certificate of Suitability has been provided covering the manufacture and control of the drug substance metformin hydrochloride. The drug substance specification complies with the Ph Eur monograph, with additional in-house controls for residual solvents and particle size. These are satisfactory.

Certificates of analysis for three batches of drug substance are provided. All meet with the required specifications and are satisfactory.

Stability data from three consecutive production scale batches show the active substance to be a physically and chemically stable drug.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients sodium starch glycollate (Type A), maize starch, povidone K30, colloidal anhydrous silica, magnesium stearate. The film-coating consisted of methylhydroxypropylcellulose, titanium dioxide E171, propylene gylcol, polyethylene glycol 6000 and purified water.

All excipients are subject of European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph/specifications. None of the excipients contain material from animal or human origin.

Pharmaceutical development
The objective of the development program was to develop a film-coated tablet containing metformin hydrochloride that was bioequivalent to that of the originator product, Glucophage 500 and 850 mg Tablets (Marketing Authorisation Holder: Lipha Pharmacetuicals Limited, UK).

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results. Comparative impurity studies have also been undertaken.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results for three production-scale batches. These data show satisfactory consistency from batch to batch.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. 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
All strengths of tablet are packaged in polyvinylchloride/polyvinylidenechloride/aluminium blister strips in pack sizes of 20, 28, 30, 50, 56, 60, 84, 90, 100 and 120 film-coated tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

Stability of the product
Stability studies were performed on three commercial batches of each strength of finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 3 years, which is satisfactory. Storage conditions are “Store below 25 degrees”.

Bioequivalence/bioavailability
Two bioequivalence studies were performed, comparing the finished product versus the comparator product (Glucophage Tablets, Lipha Pharmaceuticals Limited, UK).

The results of the studies demonstrated acceptable bioequivalence.

Dissolution data provided by the applicant have shown that the test product is essentially similar in dissolution terms to that of the comparator product (Glucophage Tablets, Lipha Pharmaceuticals Limited, UK).

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

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

III.3 CLINICAL ASPECTS

INDICATIONS

The proposed indications are the same as those for the originator product, Glucophage, namely 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. It may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

DOSE AND DOSAGE SCHEDULE

The various treatment regimes are separately detailed in the Summary of Product Characteristics.

TOXICOLOGY

No formal data are presented and none are required for this application. The toxicological and pharmacological profile of metformin is well known and understood.

CLINICAL PHARMACOLOGY

No formal data are presented and none are required for this application, save for bioequivalence studies. The clinical expert discusses the pharmacodynamics and pharmacokinetics in adequate detail with references up to the date of the report in 1996.

Bioavailability / bioequivalence
Two bioequivalence studies between test and reference preparations of both strengths are presented, carried out in compliance with Good Clinical Practice in 1997. In each study the reference product chosen was Glucophage (Lipa Pharmaceutical Ltd, UK). These are satisfactory comparators.

Study MET(AC)-BQB-VVS-97
In this comparative, randomised, two-way, two-period, single dose crossover study, 24 healthy fasted male volunteers received 500mg orally of either the applicant's test product or the reference product Glucophage. The test product is from the same manufacturer as indicated in the MAA form. Serum drug levels were followed for 48 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period of 7 days between phases was sufficiently long.

The randomisation scheme was balanced for sequence and appears random.

Log-transformed data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA and non-parametrically. T_{max} was analysed non-parametrically.

Results
There were no major protocol deviations or discontinuations. Bioequivalence results for log-transformed test/reference ratios (ANOVA) with 90% Confidence Intervals:

AUC_t	**1.04**	**(0.98 – 1.11)**
AUC_{inf}	**1.04**	**(0.98 – 1.11)**
C_{max}	**1.02**	**(0.94 – 1.12)**
T_{max}	**2.85 hrs (test)**	**2.59 hrs (reference)**

Assessor's Comment
Bioequivalence for the 500mg strength has been satisfactorily demonstrated in accordance with CPMP criteria.

Study MET(AC)-BQA-OPM-96
In this comparative, randomised, two-way, two-period, single dose crossover study, 24 healthy fasted male volunteers received 850mg orally of either the applicant's test product or the reference product Glucophage. The test product is from the same manufacturer as indicated in the MAA form.

Serum drug levels were followed for 48 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period of 7 days between phases was sufficiently long. The randomisation scheme was balanced for sequence and appears random.

Log-transformed data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA and non-parametrically. T_{max} was analysed non-parametrically.

Results
There were no major protocol deviations or discontinuations. Bioequivalence results for log-transformed test/reference ratios (ANOVA) with 90% Confidence Intervals:

AUC_t	**0.93**	**(0.98 – 0.99)**
AUC_{inf}	**0.93**	**(0.88 – 0.99)**
C_{max}	**0.94**	**(0.84 – 1.00**
T_{max}	**3.0 hrs (test)**	**3.2hrs (reference)**

Assessor's Comment
Bioequivalence for the 850mg strength has also been satisfactorily demonstrated in accordance with CPMP criteria.

EFFICACY
No new efficacy data are presented in this application and none are required. The efficacy of metformin is well established.

SAFETY
No formal safety data are presented and none are required. There is a full review up to 1996 of known efficacy and safety data in the Clinical Expert's Report.

EXPERT REPORT
A satisfactory expert report is provided by an appropriately qualified individual.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

LABELLING
This is satisfactory.

MAA
This is satisfactory.

DISCUSSION
These applications for Metformin 500mg and 850mg have been shown to be the same (by bioequivalence studies) as the cross-reference product Glucophage 500mg and 850mg Tablets from Lipha Pharmaceuticals.

RECOMMENDATIONS
These product licences may be granted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Metformin 500 mg and 850 mg 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.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant's Metformin 500 mg and 850 mg Tablets and the originator products Glucophage 500mg and 850mg Tablets (Lipha Pharmaceuticals). These products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Glucophage Tablets.

RISK BENEFIT ASSESSMENT
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 hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
20/08/2007	Type IB variation	To add of 20, 28, 30, 50, 56, 60, 90, 100 and 120 tablet pack sizes to the product licence. Section 6.5 (Nature and content of container) of the SPC and labelling are updated	Approved 17/12/2007