Public Assessment Report

Decentralised Procedure

Metabet SR 500mg Prolonged Release Tablets

Metformin Hydrochloride

UK/H/3943/01/DC

UK licence no: PL 20117/0173

Applicant: Morningside Healthcare Limited
LAY SUMMARY

On the 16th June 2010 the MHRA granted Morningside Healthcare Limited Marketing Authorisation (licence) for the medicinal product Metabet SR 500mg Prolonged Release Tablets. This medicine is only available on prescription from your doctor.

Metabet SR tablets contain the active ingredient metformin hydrochloride. This medicine is used in the treatment of diabetes.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Metabet SR 500mg Tablets outweigh the risks. Hence, Marketing Authorisation has been granted.
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# Module 1

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Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Metabet SR 500mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each prolonged release tablet contains:
Metformin Hydrochloride 500 mg corresponding to 390 mg metformin base
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Prolonged release tablet

Off-white coloured, oval, biconvex, film coated tablets plain on both sides.

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. Metabet SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

4.2 Posology and method of administration
Adults

Monotherapy and combination with other oral antidiabetic agents
The usual starting dose is one tablet of Metabet SR 500 mg tablet once daily. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dose is 4 tablets of Metabet SR 500 mg tablet daily. Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not achieved on 2000 mg of Metabet SR once daily, of 1000 mg of Metabet SR twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

In patients already treated with metformin tablets, the starting dose of Metabet SR should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to Metformin sustained release tablets is not recommended.

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

Combination with insulin:

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose of Metabet SR is one 500 mg tablet once daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

For patients already treated with metformin and insulin in combination therapy, the dose of metformin 750mg prolonged release tablets or metformin 1000 mg prolonged release tablets should be equivalent to the daily dose of metformin tablets up to a maximum of 1500 mg or 2000 mg respectively, given with the evening meal, 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 available data, Metabet SR should not be used in children.
4.3 Contraindications
Hypersensitivity to metformin hydrochloride or to any of the excipients.
• Diabetic ketoacidosis, diabetic pre-coma.
• Renal failure or renal dysfunction (creatinine clearance < 60mL/min).
• Acute conditions with the potential to alter renal function such as:
  - dehydration
  - severe infection
  - shock
  - Intravascular administration of iodinated contrast agents (see section 4.4).
• 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, creatinine clearance (this can be estimated using the
Cockcroft-Gault formula) and/or serum creatinine levels should be determined before initiating
treatment and regularly there after:

* 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 re instituted
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 and lactation
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 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
Metabet SR 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 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000),
Not known (cannot be estimated from the available data)

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 section 4.4.).
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. 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

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 of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Blood Glucose lowering drugs, excluding Insulins Biguanides.
ATC code: A10BA02

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, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur

Clinical efficacy:
The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes in patients treated with immediate release metformin as first line therapy after diet failure.
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 the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a Tmax at 7 hours (Tmax for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that observed after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of Cmax and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both Cmax and Tmax are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

**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 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Core:
  - Stearic Acid
  - Shellac (Refined bleached)
  - Povidone K-30
  - Silica, colloidal anhydrous
  - Magnesium Stearate

- Film-Coating:
  - Hypromellose
  - Hydroxy Propyl cellulose
  - Titanium dioxide
  - Propylene Glycol
  - Macrogol 6000
6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years

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

6.5 Nature and contents of container
PVC/PVDC/Aluminium blister- Blister packs of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100 and 112 film coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0173

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATI0N
16/06/2010

10 DATE OF REVISION OF THE TEXT
16/06/2010
PAR Metabet SR 500mg Prolonged release 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 Metabet SR is and what it is used for
2. Before you take Metabet SR
3. How to take Metabet SR
4. Possible side effects
5. How to store Metabet SR
6. Further information

Module 3

1. WHAT IS METABET SR AND WHAT IT IS USED FOR
Metabet SR prolonged release tablets contain the active ingredient metformin hydrochloride. Each tablet contains 500 mg of metformin hydrochloride. Metformin belongs to a group of drugs called biguanides which are used in the treatment of diabetes.

Metabet SR 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) in your blood because your pancreas does not produce enough insulin or because it produces insulin that does not work properly.

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

2. BEFORE YOU TAKE METABET SR

Do not take Metabet SR
• If you are 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 have fainted or suffered a coma due to your diabetes.
• 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.
• If you are under the age of 18 years.

Take special care with Metabet SR
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). Your doctor may also perform these tests when starting treatment for high blood pressure.

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.

You should avoid drinking alcohol and using alcohol containing medicines as this will increase the risk of lactic acidosis.

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

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

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

Taking Metabet SR alone does not normally cause low blood sugar levels (hypoglycaemia). Taking Metabet SR 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 Metabet SR may be altered by:
• Steroids such as prednisolone, mometasone, budesonide
• Beta-2-agonists such as salbutamol used for asthma
• Diuretics (water tablets) such as bendrofluindione
• ACE inhibitors such as lisinopril, enalapril used for blood pressure

Taking Metabet SR 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 drinking alcohol while taking Metabet SR.

Pregnancy and breast-feeding
Do not take Metabet SR if you are pregnant or breast-feeding. Tell your doctor immediately if think you are pregnant.
PAR Metabet SR 500mg Prolonged release Tablets

Driving and using machines:
Metabet SR 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 METABET SR

Always take Metabet SR 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 500 mg tablet daily with your evening meals. After two weeks your doctor may increase the dose to a maximum of 2000 mg per day. In some cases, your doctor may recommend that you take the tablet twice a day. Always take the tablets with food and swallow whole (without chewing or breaking), with a glass of water.

Children and adolescents below 18 years: The use of the medication is not recommended.

Your doctor will test your blood glucose and your kidney function at intervals while you are taking Metabet SR 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 Metabet SR.

If you take more Metabet SR than you should
Tell your doctor or contact the nearest hospital, taking the medicine or this leaflet with you. If the overdose is large, "lactic acidosis" is more likely and this is a medical emergency requiring treatment in hospital.

If you forget to take Metabet SR
Take the missed dose as soon as you remember, unless it's nearly time for the next one. Do not take a double dose to make up for a forgotten dose. Take the remaining doses at the correct time.

If you stop taking Metabet SR
If you stop taking Metabet SR, 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 Metabet SR 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.

The following side effects have also been reported:

Very common (affecting more than one person in 10):
- Stomach pains or stomach upsets such as nausea, vomiting, diarrhoea, loss of appetite. 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.

Common (affecting less than one person in 10 but more than one person in 100):
- Taste disturbance.

Very rare (affecting less than one in 10,000):
- Skin rash (redness and itching of the skin, hives).
- Liver problems (hepatitis), possibly with jaundice (yellowing of skin and eyes) which goes away on stopping Metabet SR.
- A decrease in vitamin B12 absorption, which can result in anaemia, sore tongue, tingling and numbness.

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

5. HOW TO STORE METABET SR

Keep out of the reach and sight of children. Do not take Metabet SR after the expiry date printed on the blister pack and carton. The expiry date (EXP) refers to the last day of that month.

Do not store above 30°C.

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

6. FURTHER INFORMATION

What Metabet SR contains
The active substance is metformin hydrochloride. Each prolonged release tablet contains 500 mg of metformin hydrochloride. The other ingredients in the tablets are Stearic Acid, Shellac (Refined bleached), Povidone K-30, Silica Colloidal Anhydrous, Magnesium Stearate, Hypromellose, Hydroxy Propyl cellulose, Titanium Dioxide, Propylene Glycol, Macrogol 6000, and Talc.

What Metabet SR looks like and contents of the pack
Metabet SR 500 mg tablets are off-white coloured, oval, biconvex, film coated tablets plain on both sides.

Metabet SR is available in blister packs of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100 and 112 tablets.

Not all pack sizes may be marketed

Marketing Authorisation Holder:
Morningside Pharmaceuticals Ltd
115 Narborough Road
Leicester, LE3 0PA
United Kingdom

Site responsible for batch release:
Morningside Healthcare Ltd
5 Pavilion Way, Loughborough, LE11 5GW
United Kingdom

This leaflet was last updated in:
June 2010
Module 4
Labelling

Metabet SR
500mg Prolonged Release Tablets
(Metformin Hydrochloride)
Morningside Healthcare Ltd

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500mg Prolonged Release Tablets
(Metformin Hydrochloride)
Morningside Healthcare Ltd
Each prolonged release tablet contains metformin hydrochloride 500 mg corresponding to 350 mg metformin base.

**DOSAGE:** To be taken as directed by the doctor. The tablets should be swallowed whole.

For oral use.

Read the package leaflet before use.

**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**

Do not store above 30°C.
PAR Metabet SR 500mg Prolonged release Tablets

Each prolonged release tablet contains metformin hydrochloride 500 mg corresponding to 390 mg metformin base.

**Dosage:** The tablets are intended for oral use. The tablets should be swallowed whole.

Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Store at or below 30°C.
Module 5

Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Metabet SR 500mg Prolonged Release Tablets in the 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. Metabet SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin is approvable.

This is a decentralised application submitted as standard abridged application in accordance with Article 10.1 of Directive 2001/83/EC as amended. The reference medicinal product is Glucophage 500 mg film coated tablets by Lipha Pharmaceuticals Limited authorised in 1983 in the UK (PL 03759/0012). Glucophage SR 500 mg prolonged release tablets, PL 11648/0054, marketed by Merck Serono Ltd are used as comparator for purposes of evaluation of bioequivalence.

With UK as the Reference Member State in this Decentralised Procedure, Morningside Healthcare Limited is applying for the Marketing Authorisation for Metabet SR 500mg Prolonged Release Tablets in IE.

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.

The submitted dossier is of an acceptable standard.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, of 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.
# ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Metabet SR 500mg Prolonged Release Tablets |
| Name(s) of the active substance(s) (INN) | Metformin Hydrochloride |
| Pharmacotherapeutic classification (ATC code) | A10BA02 – Oral anti-diabetics |
| Pharmaceutical form and strength(s) | Prolonged release tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/3943/01/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | IE |
| Marketing Authorisation Number(s) | PL 20117/0173 |
| Name and address of the authorisation holder | Morningside Healthcare Limited, 115 Narborough Road, Leicester LE3 OPA, UK |
SCIENTIFIC OVERVIEW AND DISCUSSION

II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: Metformin Hydrochloride
Chemical Name: 1) Imidodicarbonimidic diamide, N,N-dimethyl-, monohydrochloride
2) 1,1-Dimethylbiguanide monohydrochloride

Structure:

```
\begin{center}
\begin{tikzpicture}
\node[above] at (0,0) {\text{Molecular Formula: C$_4$H$_{11}$N$_5$ HCl}};
\node[above] at (0,-0.5) {\text{Molecular Weight: 165.62}};
\node[above] at (0,-1) {\text{Appearance: white crystals}};
\node[above] at (0,-1.5) {\text{Solubility: Freely soluble in water; slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride.}};
\end{tikzpicture}
\end{center}
```

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

Appropriate stability data have been generated, supporting a suitable retest period for active metformin hydrochloride when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients stearic Acid, shellac (Refined bleached), povidone K-30, silica, colloidal anhydrous, magnesium stearate, hypromellose, hydroxy propyl cellulose, titanium dioxide, propylene glycol, macrogol 6000 and talc purified.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of shellac and stearic acid, which is controlled by in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. A declaration is provided that shellac, magnesium stearate and titanium dioxide are not animal origins.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been compared with that of the originator product and these are similar.

Manufacture

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

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and 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**
The tablets are packed in PVC/PVDC/Aluminium blister. Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years with a storage condition ‘Do not store above 30 °C’ is set with a storage condition.

**Bioequivalence/bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Bioequivalence has been demonstrated between the test and reference product (see clinical assessment).

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Conclusion**
It is recommended that Marketing Authorisation is granted for this application.

The requirements for a generic product of the originator product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator product.

**III. PRE-CLINICAL ASPECTS**
This application claim to be generic medicinal product of Metabet SR 500mg prolonged release tablets, which has been licensed within the EU for over 10 years.

No new preclinical data have been supplied with this application. However, a preclinical expert report summarising relevant non-clinical studies has been included in the dossier. This is satisfactory.
A suitable justification has been provided for non-submission of an environmental risk assessment.

IV. CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
To support the application, the applicant has submitted two bioequivalence studies: EM/07/011 (fasting) and EM/07/022 (fed).

Study EM/07/011 (Fasting)
This was an open label, randomised, two-period, two-treatment, two-sequence, single dose crossover design study. The study complied with requirements of GCP. After an overnight fast of at least 10 hours, subjects were administered a single oral dose of either the test or the reference product with 240 mL of 20% glucose solution in water.

A total of 40 healthy subjects were enrolled in the study. Subject no.20 was withdrawn before dosing in period II, due to occurrence of adverse events. Subject no.19 was withdrawn after 36.00 hours post-dose sample collection in period II, due to adverse events. In all 38 subjects completed the clinical phase of the study. Subject 19 was included in analysis as only one sample was missed (48.00 hours post-dose sample in period II). In total plasma samples of 39 subjects (excluding subject 20) were analysed.

Results

<table>
<thead>
<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-inf}</td>
<td>5562.95</td>
<td>102.33</td>
<td>92.59, 113.09</td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>5275.32</td>
<td>104.38</td>
<td>94.73, 115.01</td>
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<tr>
<td>C_{max}</td>
<td>689.45</td>
<td>114.83</td>
<td>107.30, 122.88</td>
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</table>

*Geometric mean has been taken as the antilog (exponential) of the Least square mean of the log-transformed data.

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>90% Confidence Interval for Log-transformed data</th>
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<td>5578.49</td>
<td>99.60</td>
<td>90.96, 109.06</td>
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<tr>
<td>AUC_{0-t}</td>
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<td>93.12, 110.31</td>
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<tr>
<td>C_{max}</td>
<td>690.78</td>
<td>112.19</td>
<td>106.08, 118.65</td>
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</table>

Table of Geometric Means and 90% Confidence Interval Including subject no. 9 (N=39)

Table of Geometric Means and 90% Confidence Interval Excluding subject no. 9 (N=38)
The 90% confidence intervals for $C_{\text{max}}$, $\text{AUC}_0$-$\text{t}$ and $\text{AUC}_0$-$\text{inf}$ are within the acceptable range of 80 to 125% irrespective of inclusion/exclusion of subject 9. Bioequivalence of the test product in fasting state has been shown.

**Study EM/AHD/07/022 (Fed)**

This was a randomised, open label, two-period, two-treatment, two-sequence, single dose, crossover bioequivalence study in normal healthy human male subjects, under fed condition. Tablets were administered tablets 30 minutes after a high fat breakfast. Tablets were administered with 240ml of 20% glucose solution. The sampling period was upto 48 hours post dose.

A total of 68 normal, healthy adult male subjects (aged 18 – 55 years) were enrolled in the study 2 dropped out, 2 were withdrawn, due to adverse events and intolerance to high fat meal.

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>A/B</td>
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<tr>
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<tr>
<td>$C_{\text{max}}$</td>
<td>664.45</td>
<td>633.99</td>
<td>104.80</td>
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</table>

*Geometric mean has been taken as the antilog (exponential) of the Least square mean of the log-transformed.

Bioequivalence of the test product in fed state has been shown.

Based on the submitted bioequivalence studies Metabet SR 500 mg Prolonged Release Tablet is considered bioequivalent with Glucophage SR 500 mg Prolonged Release Tablet.

**Pharmacodynamics**

The pharmacodynamic characteristics of metabet have been well-studied in the past. There would be no particular concerns for a generic medicinal product.

**Clinical Efficacy**

No new data have been submitted and none are required.

**Clinical Safety**

No new data have been submitted and none are required.

**Expert Reports**

A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of Module 5.
Conclusion
The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval of marketing authorisation is recommended from a clinical point of view.

Module 1 – Administrative information
MAA forms
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SPC)
The SPCs are medically satisfactory and consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.

Packaging
The packaging is medically satisfactory.

Pharmacovigilance System
The RMS considers that the Pharmacovigilance system as described by the Applicant generally fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
The RMS considers that the Risk Management Plan submitted is satisfactory.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Metabet SR 500mg Prolonged Released 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 an application of this type.

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

The SPC and PIL are satisfactory and consistent with that of the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Metabet SR 500mg Prolonged Released Tablets 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**

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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