Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Glucient SR 500mg Prolonged Release Tablets Metformin hydrochloride

UK/H/2813/001/DC

UK licence no: PL 24837/0017

Consilient Health Limited

LAY SUMMARY

On 21st February 2011, the Concerned Member States (CMSs) and the Reference Member State (RMS) agreed to grant Marketing Authorisation to Consilient Health Limited for the medicinal product Glucient SR 500mg Prolonged Release Tablets. The marketing authorisation was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 3rd March 2011. This medicine is only available on prescription from your doctor.

Glucient SR contains the active substance metformin hydrochloride that belongs to a group called biguanides, which are used to treat diabetes by regulating the level of sugar in the blood.

Glucient SR is used in patients who have non-insulin-dependent (type 2) diabetes, particularly in overweight patients, where diet and exercise alone have failed to control it. Metformin can be given alone or in combination with other oral glucose lowering medicines or with insulin.

Glucient SR is a prolonged-release medicine. This means that the release of the medication is spread over a longer period of time than an immediate-release medicine.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Glucient SR 500mg Prolonged Release Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Glucient SR 500mg Prolonged Release Tablets
Type of Application	Generic, Article 10.1
Active Substance	Metformin hydrochloride
Form	Prolonged Release Tablets
Strength	500mg
MA Holder	Consilient Health Limited, 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland
RMS	UK
CMS	Czech Republic, Hungary and Latvia
Procedure Number	UK/H/2813/001/DC
Timetable	Day 187 – 21st February 2011

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glucient SR 500mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 500 mg metformin hydrochloride (equivalent to 390 mg metformin).

Excipients

Each prolonged release tablet contains up to 10.8mg sodium (0.5mmol)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White, convex, capsule-shaped tablet marked “XR” on one side.

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

4.2 Posology and method of administration

Posology

Monotherapy and combination with other oral antidiabetic agents:

• The usual starting dose is one tablet of 500 mg 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 500 mg 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 Glucient SR once daily, 1000 mg of Glucient 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 Glucient 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 Glucient SR is not recommended.

• If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Glucient 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 Glucient SR is one tablet of 500 mg once 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 available data, Glucient SR should not be used in children.

Method of administration

The tablets should be swallowed whole with a drink of water. They should not be chewed or crushed.

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 < 60 ml/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 (see section 4.6).

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 and/or 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 creatinine clearance levels at the 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 under general, spinal or peridural anaesthesia. Therapy should be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if renal function has been established.

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 sulphonylureas.

Excipients

Each tablet contains up to 10.8mg sodium (0.5mmol) which should be taken into consideration for patients on a controlled sodium diet

4.5 Interaction with other medicinal products and other forms of interaction

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

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 (see section 4.4).

Associations 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 fetal 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 fetal 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

Glucient 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 (sulphonylureas, insulin, repaglinide).

4.8 Undesirable effects

In post marketing data and in controlled clinical studies, adverse event reporting in patients treated with Glucient SR was similar in nature and severity to that reported in patients treated with Metformin immediate-release.
The following undesirable effects may occur with metformin.
Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000, not known (cannot be estimated from the available data).
Metabolism and nutrition disorders
Very rare: Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia.
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
Not known: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders
Very rare: Skin reactions such as erythema, pruritus, urticaria

4.9 Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85 g, 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

Pharmacotherapeutic group: Oral blood glucose lowering drugs, 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) and delay of intestinal glucose absorption.
Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin increases the transport capacity of all types of membrane glucose transporters (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 overweight type 2 diabetic 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 sulphonylurea 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 sulphonylurea 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 sulphonylurea, 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 2000 mg of Metformin prolonged-release tablets is similar to that observed after administration of 1000 mg 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).
Metformin absorption from the prolonged-release formulation is not altered by meal composition. No accumulation is observed after repeated administration of up to 2000 mg 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
Cellulose, microcrystalline
Carmellose sodium
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

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

6.5 Nature and contents of container
PVC/PVDC aluminium blisters.
Blister packs of 28, 30, 56, 60 & 100 prolonged-release tablets.
Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Consilient Health Limited,
5th Floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 24837/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/03/2011

10 DATE OF REVISION OF THE TEXT
03/03/2011

Module 3

CONSILIENT HEALTH Ltd.

PACKAGE LEAFLET
INFORMATION FOR THE USER

Glucient® SR 500 mg 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.
- 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 you have any further questions, ask your doctor or pharmacist. 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.

In this leaflet:

1. WHAT IS GLUCIENT SR AND WHAT IS IT USED FOR

The name of this medicine is Glucient SR 500 mg prolonged-release tablets, which is referred to as Glucient SR throughout this leaflet.

Glucient SR contains the active substance metformin hydrochloride that belongs to a group of active substances called biguanides, which are used to treat diabetes by regulating the level of sugar in the blood.

Glucient SR is used in patients who have non-insulin-dependent (type 2) diabetes, particularly in overweight patients, where diet and exercise alone have failed to control it. Metformin can be given alone or in combination with other oral antidiabetic medicines or with insulin.

Glucient SR is a prolonged-release medicine. This means that the release of the medication is spread over a longer period of time than an immediate-release medicine.
Ask your doctor or pharmacist if you need additional information.

2. BEFORE YOU TAKE GLUCIENT SR

Do NOT take Glucient SR:
- if you are allergic (hypersensitive) to metformin hydrochloride or any of the other ingredients in this medicine (listed below in section 6)
- if you have diabetic ketoacidoisis (a complication of diabetes which may be associated with frequent urination, feeling and being sick, abdominal pain, lethargy and sleepiness) or diabetic pre-coma (altered mental state due to an imbalance in blood sugar)
- if you have kidney or liver problems
- if you are dehydrated
- if you are suffering from a severe infection
- if you are going to have a certain type of X-ray with an injectable dye – see below under 'Taking other medicines'
- if you have recently suffered from heart failure
- if you have recently had a heart attack, have circulatory problems or breathing difficulties
- if you are a heavy drinker
- if you are breast-feeding.

Take special care with Glucient SR
Treatment with Glucient SR may rarely cause a serious condition called lactic acidosis (where there is too much acid in the blood) which requires urgent hospital treatment to prevent it leading to coma. Other illnesses, prolonged fasting, poor blood sugar control, or alcohol intake can all increase the risk of lactic acidosis developing. You should be aware of the warning symptoms which include muscle cramps, abdominal pain, breathlessness and a feeling of being very weak and unwell. If you develop these symptoms you must tell your doctor immediately. Your doctor should check that your kidneys are working properly at least once a year or more often if needed.

If you are going to have an anaesthetic, x-ray or scan, tell your doctor that you are taking Glucient SR. It is advisable to stop taking Glucient SR for 48 hours before and after the procedure.

Continue to follow any dietary advice your doctor has given you and get some regular exercise while you are taking this medicine.

Be careful if you are taking Glucient SR with insulin or other antidiabetic medicines, as the combination may increase the risk of hypoglycaemia (excessively low sugar in your blood).

Children and adolescents should not take Glucient SR.

Taking other medicines
Glucient SR must not be used at the same time as some injectable dyes used for certain kinds of 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 Glucient SR. It is advisable to stop taking Glucient SR for 48 hours before and after the procedure.

Glucocorticoids (e.g. budesonide, beclometasone or hydrocortisone, which are sometimes used to suppress inflammation caused by allergic reactions and in asthma), beta-2-agonists (e.g. salbutamol, which are used in the treatment of asthma) and diuretics (water tablets which increase urine production and may be used to treat high blood pressure) can all increase blood sugar levels. You should check your blood sugar more often if you are taking Glucient SR with any of these medicines.

ACE (Angiotensin Converting Enzyme) inhibitors (e.g. quinapril or captopril, which are used to treat heart problems) can reduce blood sugar levels.

The use of diuretics, other treatments for high blood pressure or NSAIDs (non-steroidal anti-inflammatory drugs, e.g. ibuprofen) may increase the risk of kidney problems.

Please tell your doctor or pharmacist if you are taking any of the above or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Glucient SR with food and drink
Taking your tablet with food can reduce unwanted side effects. Glucient SR must be taken during or after your evening meal.

You must avoid consuming alcohol and using alcohol-containing medicines whilst on Glucient SR, as you could be at greater risk of developing lactic acidosis, a serious complication which can be recognised by muscle cramps, abdominal pain, breathlessness and a feeling of being very weak and unwell (please see 'Do NOT take Glucient SR').

Pregnancy and breast-feeding
Tell your doctor if you are, think you might be or are planning to become pregnant. During pregnancy, diabetes should be treated with insulin. If you find out that you are pregnant while taking Glucient SR, consult your doctor so that they may change your treatment.
Do not take Glucient SR if you are breast-feeding or if you are planning to breast-feed your baby.

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

Driving and using machines
Taking Glucient SR does not affect your ability to drive or use machines. However, there is an increased risk of low blood sugar levels if Glucient SR is taken with other medicines for diabetes (sulphonylureas, insulin or repaglinide). This may cause dizziness and fainting. Do not drive or operate machines if you are affected.

Important information about some of the ingredients of Glucient
This medicinal product contains up to 1.9 mmol (or 43.2 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE GLUCIENT SR

Always take Glucient SR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Swallow the tablet whole with a drink of water during or after your evening meal. Do not chew or crush the tablet.

The usual doses are explained below.

Adults:
For patients taking Glucient SR by itself or combined with other oral antidiabetic medicines:
The usual starting dose is one tablet of 500 mg once a day. After 10 to 15 days, your doctor will adjust the dose on the basis of blood glucose measurements. Your doctor may increase the dose up to a maximum of 2,000 mg of metformin hydrochloride per day (four of these 500 mg Glucient SR tablets in one day).

For patients already taking Metformin and switching to Glucient SR:
The usual starting dose of Glucient SR should be equal to your daily dose of metformin immediate-release tablet.

For patients taking Glucient SR combined with insulin:
When taking Glucient SR with insulin, the usual starting dose is one tablet of 500 mg once a day, while insulin dosage is adjusted on the basis of blood sugar measurements.

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

Children and Adolescents:
This medicine is not recommended for children and adolescents.

You should continue to take these tablets for as long as your doctor tells you to.

If you take more Glucient SR than you should
If you or someone else takes too much Glucient SR, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

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

If you stop taking Glucient SR
If you stop treatment with Glucient SR without medical advice, you have to be aware of an uncontrolled increase in blood sugar levels. Late symptoms of diabetes, such as damage to the eyes, kidneys and vessels, may occur.

If you see another doctor or go into hospital, let them know what medicines you are taking.

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

4. POSSIBLE SIDE EFFECTS

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

If you experience any of the following, contact your nearest hospital casualty department or your doctor immediately:
If you have symptoms which include muscle cramps, stomach pain, breathlessness and a feeling of being very weak and unwell; this could indicate you have lactic acidosis, a serious but very rare side effect of metformin.

The following side effects have been reported at the approximate frequencies shown:

Very common (affecting more than 1 person in 10):
- Nausea (feeling sick)
- Vomiting
- Diarrhoea
- Abdominal pain (stomach pain)
- Loss of appetite.

Common (affecting less than 1 person in 10 but more than 1 person in 100):
- Taste disturbances.

Very rare (affecting less than 1 person in 10,000):
- Decrease in vitamin B12: Over time this may lead to anaemia, a sore mouth or tongue, or possibly numbness or tingling in the limbs.
- Redness and itching of the skin, hives (nettle rash)
- There have also been isolated reports of liver problems, including hepatitis (jaundice: yellowing of the skin or eyes).

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 GLUCIENT SR

Keep out of the reach and sight of children.

Do not store above 30°C. Do not use Glucient SR after the expiry date that is stated on the blister and the carton. The expiry date refers to the last day of the month.

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 Glucient SR contains
- The active substance is metformin hydrochloride. Each prolonged-release tablet contains 500 mg of metformin hydrochloride corresponding to 390 mg of metformin.
- The other ingredients are microcrystalline cellulose 102, carmellose sodium 2000, hypromellose 100M, colloidal anhydrous silica and magnesium stearate.

What Glucient SR looks like and contents of the pack:
- Glucient SR 500 mg prolonged-release tablets are white, convex, capsule-shaped tablets marked "XR" on one side.
- The tablets are available in pack sizes of 28, 30, 56, 60 and 100 tablets.

Not all pack sizes may be marketed.

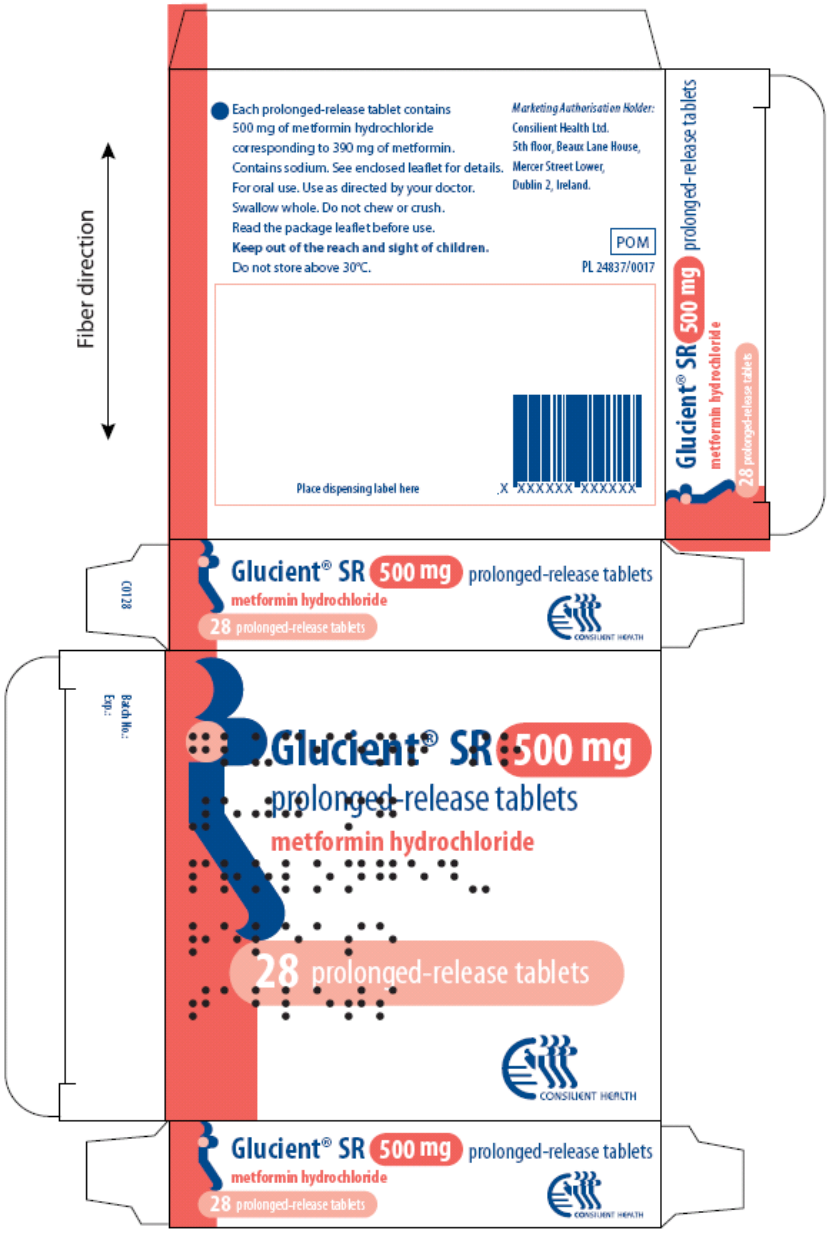
Marketing Authorisation Holder
Consilient Health Ltd., 5th floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland

Manufacturer
McGregor Cory Limited, Middleton Close, Banbury, Oxon, OX16 4RS

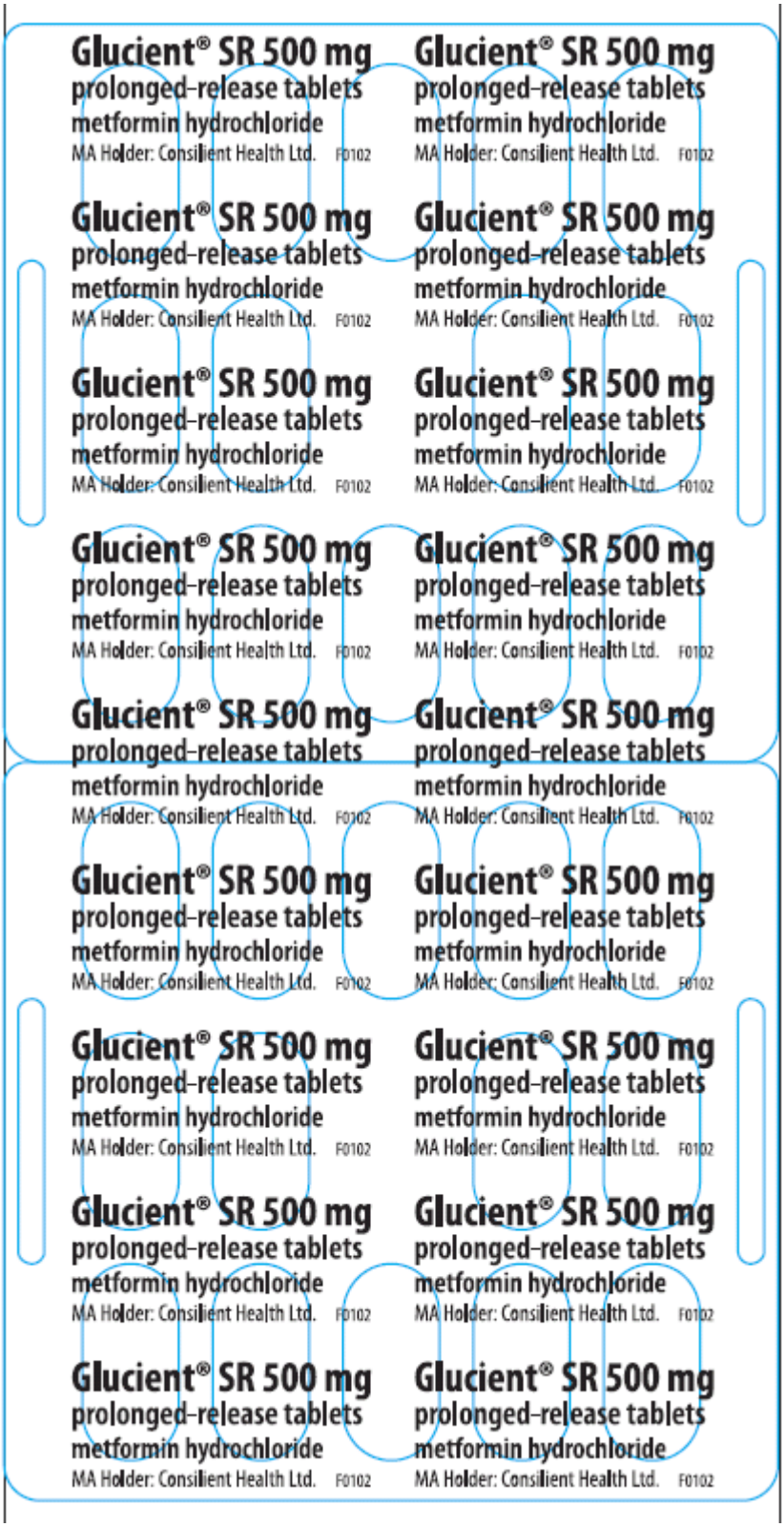
This leaflet was last revised in November 2010.

PL 24837/0017 P0078

Module 4
Labelling




Each prolonged-release tablet contains 500 mg of metformin hydrochloride corresponding to 390 mg of metformin.
Contains sodium. See enclosed leaflet for details.
For oral use. Use as directed by your doctor.
Swallow whole. Do not chew or crush.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 30°C.
Marketing Authorisation Holder:
Consilient Health Ltd.
5th floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2, Ireland.
POM
PL 24837/0017
Place dispensing label here
Fiber direction
Glucient® SR 500 mg
prolonged-release tablets
metformin hydrochloride
56 prolonged-release tablets


Glucient® SR 500 mg
prolonged-release tablets
metformin hydrochloride
MA Holder: Consilient Health Ltd. F0102

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Glucient 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 glycaemic control, could be approved.

This application was submitted under Article 10.1, claiming to be generic medicinal product of Glucophage 500 mg Film-coated tablets (PL 03759/0012), which was first licensed to Lipha Pharmaceuticals, UK on 21st September 1982.

With the UK as the RMS in this Decentralised Procedure (UK/H/2813/01/DC), Consilient Health Limited applied for the Marketing Authorisation for Glucient SR 500mg Prolonged Release Tablets in Czech Republic, Hungary and Latvia.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and Post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

No new preclinical and clinical studies were conducted, which is acceptable given that the application was based on being generic medicinal product of an originator product that has been licensed for over 10 years. Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All Member States agreed to grant respective licence for the above product at the end of procedure (Day 187 – 21st February 2011). After a subsequent national phase, the UK granted a licence for this product on 3rd March 2011 (PL 24837/0017).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Glucient SR 500mg Prolonged Release Tablets
Name(s) of the active substance(s) (INN)	Metformin hydrochloride
Pharmacotherapeutic classification (ATC code)	A10BA02
Pharmaceutical form and strength(s)	Prolonged Release Tablets
Reference numbers for the Decentralised Procedures	UK/H/2813/001/DC
Reference Member State	United Kingdom
Concerned Member States	Czech Republic, Hungary and Latvia
Marketing Authorisation Number(s)	PL 24837/0017
Name and address of the authorisation holder	Consilient Health Limited, 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland

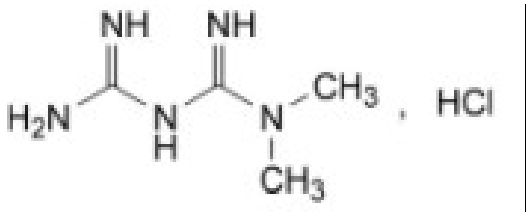
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Metformin Hydrochloride
Chemical Name: N,N-Dimethyl imido-dicarbonimidicdiamide *)1,1-Dimethyl Biguanide *)N-N Dimethyl Diguanide *)N' – Dimethyl guanylguanidine*) As hydrochloride

Structure:



Molecular Formula: $C_4H_{12}CIN_{15}$
Molecular Weight: 165.6
Appearance: White or almost white crystals. Freely soluble in water, slightly soluble in alcohol and practically insoluble in acetone and in methylene chloride.

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.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients cellulose microcrystalline, carmellose sodium, hypromellose, silica colloidal anhydrous and magnesium stearate

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

It had been confirmed that the excipients used are free of TSE/BSE and the corresponding certificates issued by each supplier were suitably provided. This is acceptable.

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Glucophage 500mg Film-coated Tablets.

Comparative impurity and dissolution profiles have been presented for test and reference products.

Manufacture

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

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

Container-Closure System
The finished product is packed in PVC/PVDC aluminium blisters. Pack sizes are 28, 30, 56, 60 and 100 prolonged-release tablets.

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. Based on the results, a shelf-life of 36 months with a storage condition of 'Do not store above 30ºC' has been set and these are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labels are pharmaceutically acceptable.

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

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

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

III.2 PRE-CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of metformin hydrochloride are well-known.

No new preclinical data have been supplied with this application and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

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

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

III.3 CLINICAL ASPECTS

Clinical Pharmacology

Pharmacokinetics

In support of this application, the marketing authorisation holder has submitted four bioequivalence studies under fast and fed conditions.

1. Pilot Bioequivalence study (fasted)

This is a randomised open label single dose, two treatment, two period, two sequence cross over comparative bioavailability study of Glumin XR 500mg Tablets (test) and Glucophage SR 500mg Tablets (reference) in 12 healthy, male and female volunteers under fasted conditions.

A single dose of the investigational products (1 tablet of 500 mg) was administered orally to each subject in each period after a supervised overnight fast. A washout period of one week was maintained.

Serial blood sampling before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 12 and 24 hours after drug administration was carried out in each group.

Table 1. Pharmacokinetic Summary data for Metformin (N=12)

	Test	(SD)	Reference	(SD)	Geom Ratio (%)	Lower 90% CI (%)	Upper 90% CI (%)
AUCt (ng.h/mL)	6031.55	3145.39	5569.97	2682.96	107.97	93.95	124.08
AUCinf (ng.h/mL)	6366.58	3231.5	6087.58	2752.5	104.06	90.59	119.54
Cmax (ng/mL)	790.32	341.1	808.9	313.13	96.99	82.00	114.72
Tmax (h)	4	2.0-6.0	4	2.0-5.0			
Thalf (h)	4.22	1.76	4.13	2.41			

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Glumin XR 500mg Tablets) and the reference formulation (Glucophage SR 500mg Tablets) for single dose under fasted conditions.

2. Single Dose fed study

This is a randomised open label single dose, two treatment, two period, two sequence cross over comparative bioavailability study of Glucient SR 500mg Tablets (test) and Glumin XR 500mg Tablets (reference) in 24 healthy, male and female volunteers under fed conditions.

A single dose of the investigational products (1 tablet of 500 mg) was administered orally to each subject in each period with 200 ml of water after a supervised overnight fast of at least 10 hours, the subjects received a high fat, high calorie breakfast on the mornings of Period 1 and Period 2.

Serial blood sampling before dosing and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16 and 24 hours after drug administration was carried out in each group. A washout period of 14 days was maintained between the two dosing days in each group.

Table 2 Relative BioavAility Analysis of Glumin XR 500 mg tablets versus Glucophage SR 500 mg tablets for Metformin

Parameter	90% C.I. (%)	Ratio of Means (%)	Intra-Subject CV (%)
Log AUC_{0-t}	92.81-108.09	100.16	9.17
Log $AUC_{0-\infty}$	92.32-107.64	99.69	9.22
Log Cmax	105.78-118.17	111.80	7.35

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Glumin XR 500mg Tablets) and the reference formulation (Glucophage SR 500mg Tablets) for single dose under fed conditions.

3. Combined Single and Multiple Study Fasted

This is an open label, combined single and multiple dose, randomized, two-period, two-treatment, two-sequence, crossover comparative bioavailability study of Glumin XR 500mg Tablets (test) and Glucophage SR 500mg Tablets (reference) in 24 healthy, male and female volunteers under fasted conditions.

The treatment was consisted of 2 periods of 2 phases each. Each period included a single dose administration phase under fasted condition followed by multiple administrations phase of single daily fasted administrations

Blood samples were collected prior to study drug administration and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16 and 24 hours post-dose. A washout period of 9 days was maintained between two periods.

Table 3 Relative Bioavailability Analysis of Glumin XR 500 mg versus Glucophage SR 500 mg tablets for Metformin – Day 1-2 (N=24)

Parameter	90% C.I. (%)	Ratio of Means (%)	Intra-Subject CV (%)
Log AUC_{0-t}	98.48-123.24	110.17	9.80
Log $AUC_{0-\infty}$	97.63-121.61	108.96	9.64
Log C_{max}	99.24-129.33	113.29	11.58

Table 4 Relative Bioavailability Analysis of Glumin XR 500 mg vs Glucophage SR 500 mg tablets for Metformin – Day 5-6 (N=23)

Parameter	90% C.I. (%)	Ratio of Means (%)	Intra-Subject CV (%)
Log AUC_{0-t}	98.08-120.90	108.89	8.94
Log $AUC_{0-\infty}$	99.67-121.69	110.13	8.54
Log C_{max}	96.24-127.83	110.92	12.13

The results of the study showed that AUC lie within the acceptance criteria range of 80-125% in both phases of the study (Single dose and multiple dose). However C_{max} of the test product was outside the acceptance range in both phases of the study (single dose and multiple dose).

4. Combined Single Fasted and Multiple Fed Study

A combined single dose study under fasted conditions and multiple dose study under fed conditions (normal diabetic meal) comparing the bioequivalence of Glumin XR 500mg Tables (test) and Glucophage SR 500mg tablets (reference) in 40 healthy male and female volunteers.

The treatment consisted of 2 periods of 2 phases each. Each period included a single dose administration phase under fasted condition followed by multiple dose phase under fed conditions with normal diabetic meal.

Blood samples were collected prior to study drug administration and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours post-dose. A washout period of 7 days was maintained between the two periods.

Table 5 Summary of bioequivalence data for metformin in single dose administration

Parameter	Geometric Mean Ratio (90% CI)	Bioequivalence criteria
- AUC_t	110.64% (99.59 – 122.93%)	90% CI : 80 – 125%
- AUC_{inf}	109.40% (98.92 – 120.99%)	90% CI : 80 – 125%
- C_{max}	111.80% (100.62 – 124.22%)	90% CI : 80 – 125%

Table 6 Summary of bioequivalence data for metformin in multiple doses administration

Parameter	Geometric Mean Ratio (90% CI)	Bioequivalence criteria
- AUC_{tau}	105.61% (100.95 – 110.49%)	90% CI : 80 – 125%
- C_{max}	110.09% (106.59 – 113.71%)	90% CI : 80 – 125%
- C_{min}	91.06% (81.61 – 101.60%)	90% CI : 80 – 125%

In

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulation (Glumin XR 500mg Tablets) and the reference formulation (Glucophage SR 500mg Tablets) for both phases of the study (single dose fast and multiple dose fed).

Conclusion
In study 3 with multiple dose under fasted conditions, the results of C_{max} were outside the acceptance criteria range, however in study 4 with multiple doses under fed conditions (normal diabetic meal), the result of C_{max} lie within the acceptance criteria range. Study 4 under fed conditions is considered more appropriate, as it is more approximate to the conditions of a diabetic patient who does not take metformin under fasting conditions but takes it under fed contitions (low caloric meal recommended for diabetic patients), therefore the results of study 4 regarding C_{max} are acceptable.

Based on the submitted bioequivalence studies, the Test product (Glumin XR 500 mg tablets) has shown bioequivalence with the Reference product (Glucophage SR 500mg tablets) in single dose fast conditions, single dose fed conditions and multiple dose fed conditions with a standardized diabetic meal, more appropriate than a high fat meal.

Pharmacodynamics
No new data have been submitted and none are required for this generic application.

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 Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

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

Marketing Authorisation Application (MAA) Forms
The MAA form is medically satisfactory.

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

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Glucient SR 500mg Prolonged Release 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

Bioequivalence have been demonstrated between the applicant's Glumin XR 500mg Tablets and the reference product, Glucophage SR 500mg Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

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 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