Public Assessment Report

Decentralised Procedure

Dizalid 30mg Prolonged Release Tablets

UK/H/1823/001/DC

UK licence no: PL 20254/0013

Orifarm Generics A/S
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Orifarm Generics A/S a Marketing Authorisation (licence) for the medicinal product Dizalid 30mg Prolonged Release Tablets. This is a prescription-only medicine (POM) used to keep blood sugar at the correct level in adults with diabetes when it is not controlled by diet, physical exercise and weight loss alone.

Gliclazide 30mg prolonged release tablets belong to a group of medicines called sulphonylureas.

The test product, Dizalid 30mg Prolonged Release Tablets, has been shown to be a generic medicinal product of Diamicron® MR Tablets, 30mg which was granted to Servier Laboratories Ltd., UK on 7th December 2000. The reference medicinal product authorised for not less than 10 years is Diamicron®, 80mg Tablets (Servier Laboratories Limited, UK) licensed on 21st December 1979, over 10 years ago.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Dizalid 30mg Prolonged Release Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>Page 12</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 17</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 21</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>Page 21</td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td>Page 23</td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td>Page 25</td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td>Page 25</td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td>Page 31</td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>Page 32</td>
</tr>
</tbody>
</table>
# Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dizalid 30mg Prolonged Release Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Gliclazide</td>
</tr>
<tr>
<td>Form</td>
<td>Modified Release Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>30mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Orifarm Generics A/S</td>
</tr>
<tr>
<td></td>
<td>Energivej 15, 5260 Odense S, Denmark</td>
</tr>
<tr>
<td>RMS</td>
<td>UK</td>
</tr>
<tr>
<td>CMS</td>
<td>Denmark</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/1823/001/DC</td>
</tr>
<tr>
<td>End of Procedure</td>
<td>24th November 2009</td>
</tr>
</tbody>
</table>
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Dizalid 30 mg Prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each prolonged-release tablet contains 30 mg of gliclazide.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Prolonged-release tablet.
White to off – white, flat faced, bevelled edge, capsule shaped tablets, engraved ‘APO 30’ on one side, plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

4.2 Posology and method of administration
- Oral use.
- For adult use only.
- It is recommended that the tablet(s) be swallowed whole.

The daily dose may vary from 1 to 4 tablets per day, i.e. from 30 to 120 mg taken orally in a single intake at breakfast time.

If a dose is forgotten, there must be no increase in the dose taken the next day.

As with any hypoglycaemic agent, the dose should be adjusted according to the individual patient's metabolic response (blood glucose, HbA1c).

Initial dose:
The recommended starting dose is 30 mg daily.

If blood glucose is effectively controlled, this dose may be used for maintenance treatment. If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month except in patients whose blood glucose has not reduced after two weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment.

The maximum recommended daily dose is 120 mg.

Switching from Dizalid 80 mg Tablets to Dizalid 30 mg Prolonged-release tablets:
1 tablet of Dizalid 80 mg Tablets is comparable to 1 tablet of Dizalid 30 mg Prolonged-release tablet. Consequently the switch can be performed provided a careful blood monitoring.

Switching from another oral antidiabetic agent to Dizalid 30 mg Prolonged-release tablets:
Dizalid 30 mg Prolonged-release tablets can be used to replace other oral antidiabetic agents. The dosage and the half-life of the previous antidiabetic agent should be taken into account when switching to Dizalid 30 mg Prolonged-release tablets.

A transitional period is not generally necessary. A starting dose of 30 mg should be used and this should be adjusted to suit the patient's blood glucose response, as described above.
When switching from a hypoglycaemic sulphonylurea with a prolonged half-life, a treatment free period of a few days may be necessary to avoid an additive effect of the two products, which might cause hypoglycaemia. The procedure described for initiating treatment should also be used when switching to treatment with Dizalid 30 mg Prolonged-release tablets, i.e. a starting dose of 30 mg/day, followed by a stepwise increase in dose, depending on the metabolic response.

**Combination treatment with other antidiabetic agents:**
Dizalid 30 mg Prolonged-release tablets can be given in combination with biguanides, alpha glucosidase inhibitors or insulin.

In patients not adequately controlled with Dizalid 30 mg Prolonged-release tablets, concomitant insulin therapy can be initiated under close medical supervision.

**In the elderly (over 65):**
Dizalid 30 mg Prolonged-release tablets should be prescribed using the same dosing regimen recommended for patients under 65 years of age.

**In patients with mild to moderate renal insufficiency:**
The same dosing regimen can be used as in patients with normal renal function with careful patient monitoring. These data have been confirmed in clinical trials.

**In patients at risk of hypoglycaemia:**
- undernourished or malnourished,
- severe or poorly compensated endocrine disorders (hypopituitarism, hypothyroidism, adrenocorticotropic insufficiency),
- withdrawal of prolonged and/or high dose corticosteroid therapy,
- severe vascular disease (severe coronary heart disease, severe carotid impairment, diffuse vascular disease);
  It is recommended that the minimum daily starting dose of 30 mg is used.

**Children and adolescents (under 18 years of age):**
There are no data and clinical studies available in children and adolescents.

### 4.3 Contraindications

The use of gliclazide is contraindicated in patients with:
- hypersensitivity to gliclazide or to any of the excipients, other sulphonylureas, sulphonamides.
- type 1 diabetes.
- diabetic pre-coma and coma, diabetic keto-acidosis.
- severe renal or hepatic insufficiency: in these cases the use of insulin is recommended.
- treatment with miconazole (see section 4.5).
- lactation (see section 4.6).

### 4.4 Special warnings and precautions for use

**Hypoglycaemia:**
This treatment should be prescribed only if the patient is likely to have a regular food intake (including breakfast). It is important to have a regular carbohydrate intake due to the increased risk of hypoglycaemia, if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Hypoglycaemia is more likely to occur during low-calorie diets, following prolonged or strenuous exercise, alcohol intake or if a combination of hypoglycaemic agents is being used.

Hypoglycaemia may occur following administration of sulphonylureas (see section 4.8). Some cases may be severe and prolonged. Hospitalisation may be necessary and glucose administration may need to be continued for several days.

Careful selection of patients, of the dose used, and clear patient directions are necessary to reduce the risk of hypoglycaemic episodes. Factors which increase the risk of hypoglycaemia:
- patient refuses or (particularly in elderly subjects) is unable to co-operate,
- malnutrition, irregular mealtimes, skipping meals, periods of fasting or dietary changes,
- imbalance between physical exercise and carbohydrate intake,
- renal insufficiency,
- severe hepatic insufficiency,
- overdose of Dizalid 30 mg Prolonged-release tablets,
- certain endocrine disorders: thyroid disorders, hypopituitarism and adrenal insufficiency,
- concomitant administration of certain other medicines (see section 4.5).

**Renal and hepatic insufficiency:**
The pharmacokinetics and/or pharmacodynamics of gliclazide may be altered in patients with hepatic insufficiency or severe renal failure. A hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated.

**Patient information:**
The risks of hypoglycaemia, together with its symptoms, treatment, and conditions that predispose to its development, should be explained to the patient and to family members.
The patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels.

**Poor blood glucose control:**
Blood glucose control in a patient receiving antidiabetic treatment may be affected by any of the following: fever, trauma, infection or surgical intervention. In some cases, it may be necessary to administer insulin.

The hypoglycaemic efficacy of any oral antidiabetic agent, including gliclazide, is attenuated over time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. This phenomenon is known as secondary failure which is distinct from primary failure, when an active substance is ineffective as first-line treatment. Adequate dose adjustment and dietary compliance should be considered before classifying the patient as secondary failure.

**Haematological effects:**
Treatment of patients with G6PD-deficiency with sulphonylurea agents can lead to haemolytic anaemia. Since gliclazide belongs to the class of sulphonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulphonylurea alternative should be considered.

**Laboratory tests:**
Measurement of glycated haemoglobin levels (or fasting venous plasma glucose) is recommended in assessing blood glucose control. Blood glucose self-monitoring may also be useful.

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

#### 1) The following products are likely to increase the risk of hypoglycaemia

**Contra-indicated combination**

Miconazole (systemic route, oromucosal gel):
- increases the hypoglycaemic effect with possible onset of hypoglycaemic symptoms, or even coma.

**Combinations which are not recommended**

Phenybutazone (systemic route):
- increases the hypoglycaemic effect of sulphonylureas (displaces their binding to plasma proteins and/or reduces their elimination).
- It is preferable to use a different anti-inflammatory agent, or else to warn the patient and emphasise the importance of self-monitoring. Where necessary, adjust the dose during and after treatment with the anti-inflammatory agent.

Alcohol:
- increases the hypoglycaemic reaction (by inhibiting compensatory reactions) that can lead to the onset of hypoglycaemic coma.
- Avoid alcohol or medicines containing alcohol.

**Combinations requiring precautions for use**

Potentiation of the blood glucose lowering effect and thus, in some instances, hypoglycaemia may occur when one of the following drugs is taken (with examples):
Other antidiabetic agents (insulins, acarbose, biguanides), beta-blockers, fluconazole, angiotensin converting enzyme inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, and nonsteroidal anti-inflammatory agents.

2) The following products may cause an increase in blood glucose levels

Combination which is not recommended

Danazol:
- diabetogenic effect of danazol.
- If the use of this active substance cannot be avoided, warn the patient and emphasise the importance of urine and blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic agent during and after treatment with danazol.

Combinations requiring precautions during use

Chlorpromazine (neuroleptic agent):
- high doses >100 mg per day of chlorpromazine increase blood glucose levels (reduced insulin release).
- Warn the patient and emphasise the importance of blood glucose monitoring. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with the neuroleptic agent.

Glucocorticoids (systemic and local route: intra-articular, cutaneous and rectal preparations) and tetracosactrin:
- increase in blood glucose levels with possible ketosis
- (reduced tolerance to carbohydrates due to glucocorticoids).
- Warn the patient and emphasise the importance of blood glucose monitoring, particularly at the start of treatment. It may be necessary to adjust the dose of the antidiabetic active substance during and after treatment with glucocorticoids.

Ritodrine, salbutamol, terbutaline (all intravenously):
- increased blood glucose levels due to beta-2 agonist effects.
- Emphasise the importance of monitoring blood glucose levels. If necessary, switch to insulin.

3) Combination which must be taken into account

Anticoagulant therapy (warfarin):
- Sulphonylureas may lead to potentiation of anticoagulation during concurrent treatment. Adjustment of the anticoagulant may be necessary.

4.6 Pregnancy and lactation

Pregnancy:
There are no adequate data from the use of gliclazide in pregnant women even though there are few data with other sulphonylureas.

In animal studies, gliclazide is not teratogenic.

Control of diabetes should be obtained before the time of conception to reduce the risk of congenital abnormalities linked to uncontrolled diabetes.
Oral hypoglycaemic agents are not suitable, insulin is the drug of first choice for treatment of diabetes during pregnancy. It is recommended that oral hypoglycaemic therapy is changed to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered.

Lactation:
It is not known whether gliclazide or its metabolites are excreted in breast milk. Given the risk of neonatal hypoglycaemia, the product is contra-indicated in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Patients should be made aware of the symptoms of hypoglycaemia and should be careful if driving or operating machinery, especially at the beginning of treatment.
4.8 Undesirable effects
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as:

- 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 available data)

**Blood and lymphatic system disorders:**
Rare: changes in haematology. They may include anaemia, leucopenia, thrombocytopenia, granulocytopenia. These are in general reversible upon discontinuation of gliclazide.

**Eye disorders:**
Rare: transient visual disturbances may occur especially on initiation of treatment, due to changes in blood glucose levels.

**Skin and subcutaneous tissue disorders:**
Rare: rash, pruritus, urticaria, erythema, maculopapular rashes, bullous reactions.

**Gastrointestinal disorders**
Uncommon: abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, and constipation. If these should occur they can be avoided or minimised if gliclazide is taken with breakfast.

**Metabolism and nutrition disorders:**
Common: Hypoglycaemia
As for other sulphonylureas, treatment with Dizalid 30 mg Prolonged-release tablets can cause hypoglycaemia, if mealtimes are irregular and, in particular, if meals are skipped. Possible symptoms of hypoglycaemia are: headache, intense hunger, nausea, vomiting, lassitude, sleep disorders, agitation, aggression, poor concentration, reduced awareness and slowed reactions, depression, confusion, visual and speech disorders, apathy, tremor, paresis, sensory disorders, dizziness, feeling of powerlessness, loss of self-control, delirium, convulsions, shallow respiration, Bradycardia, drowsiness and loss of consciousness, possibly resulting in coma and lethal outcome.

In addition, signs of adrenergic counter-regulation may be observed: sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia.

Usually, symptoms disappear after intake of carbohydrates (sugar). However, artificial sweeteners have no effect. Experience with other sulphonylureas shows that hypoglycaemia can recur even when measures prove effective initially.

If a hypoglycaemic episode is severe or prolonged, and even if it is temporarily controlled by intake of sugar, immediate medical treatment or even hospitalisation are required.

**Hepatobiliary disorders:**
Rare: raised hepatic enzyme levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). Discontinue treatment if cholestatic jaundice appears. These symptoms usually disappear after discontinuation of treatment.

**Class attribution effects:**
Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas.

With other sulphonylureas cases were also observed of elevated liver enzyme levels and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulphonylurea or led to life-threatening liver failure in isolated cases.

4.9 Overdose
An overdose of sulphonylureas may cause hypoglycaemia. Moderate symptoms of hypoglycaemia, without any loss of consciousness or neurological signs, must be corrected by carbohydrate intake, dose adjustment and/or change of diet. Strict monitoring should be continued until the doctor is sure that the patient is out of danger.

Severe hypoglycaemic reactions, with coma, convulsions or other neurological disorders are possible and must be treated as a medical emergency, requiring immediate hospitalisation.
If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of 50 mL of concentrated glucose solution (20 to 30 %). This should be followed by continuous infusion of a more dilute glucose solution (10 %) at a rate that will maintain blood glucose levels above 1 g/L. Patients should be closely monitored and, depending on the patient's condition after this time, the doctor will decide if further monitoring is necessary.

Dialysis is of no benefit to patients due to the strong binding of gliclazide to proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, urea derivatives
ATC code: A10B B09

Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.

In addition to these metabolic properties, gliclazide has haemovascular properties.

Effects on insulin release:
In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose.

Haemovascular properties:
Gliclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:
- a partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B2).
- an action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

5.2 Pharmacokinetic properties

Absorption:
Gliclazide is completely absorbed. Food intake does not affect the rate or degree of absorption.

Distribution:
Plasma levels increase progressively during the first 6 hours, reaching a plateau which is maintained from the sixth to the twelfth hour after administration.

Intra-individual variability is low.

The relationship between the dose administered ranging up to 120 mg and the area under the concentration time curve is linear. Plasma protein binding is approximately 95%. The volume of distribution is around 30 litres.

A single daily dose of Dizalid 30 mg Prolonged-release tablets maintains effective gliclazide plasma concentrations over 24 hours.

Metabolism:
Gliclazide is mainly metabolised in the liver and excreted in the urine: less than 1% of the unchanged form is found in the urine. No active metabolites have been detected in plasma.

Excretion:
The elimination half-life of gliclazide varies between 12 and 20 hours.

Elderly:
No clinically significant changes in pharmacokinetic parameters have been observed in elderly patients.
5.3 Preclinical safety data
Preclinical data reveal no special hazards for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long term carcinogenicity studies have not been done. No teratogenic changes have been shown in animal studies, but lower fetal body weight was observed in animals receiving doses 25 fold higher than the maximum recommended dose in humans.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Hypromellose
Stearic acid
Silica, colloidal anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
1 year.
Bottle after first opening: 60 days.

6.4 Special precautions for storage
Store below 30°C.
Blisters:
Store in the original package in order to protect from moisture.
Bottle:
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container
PVC/PVDC - Aluminium foil blisters:
7, 28, 30, 56, 60, 90, 95, 175, or 180 tablets.
HDPE bottles with PP cap and polyester/aluminium liner closure:
100, 150, 200, 250 or 300 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Orifarm Generics A/S
Energivej 15
5260 Odense S
Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 20254/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/12/2009

10 DATE OF REVISION OF THE TEXT
18/12/2009
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gliclazide 30 mg Prolonged-release tablets

(gliclazide)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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.

In this leaflet:
1. Gliclazide 30 mg Prolonged-release tablets are and what they are used for
2. Before you take Gliclazide 30 mg Prolonged-release tablets
3. How to take Gliclazide 30 mg Prolonged-release tablets
4. Possible side effects
5. How to store Gliclazide 30 mg Prolonged-release tablets
6. Further information

1. Gliclazide 30 mg Prolonged-release tablets are and what they are used for

Gliclazide 30 mg Prolonged-release tablets belong to a group of medicines called sulphonylureas.

Gliclazide 30 mg Prolonged-release tablets are used to keep blood sugar at the correct level in adults with diabetes when it is not controlled by diet, physical exercise and weight loss alone.

2. Before you take Gliclazide 30 mg Prolonged-release tablets

Do not take Gliclazide 30 mg Prolonged-release tablets
- if you are allergic (hypersensitive) to gliclazide or any of the other ingredients in this medicine (see section 6: Further Information) or to other sulphonylureas and other related drugs
- if you have insulin dependent (type 1) diabetes
- if you have ketone bodies and sugar in your urine (this may mean you have keto-acidosis), diabetic pre-coma or coma
- if you have severe kidney or liver disease
- if you are taking miconazole (a treatment for fungal infections)
- if you are breast-feeding.

Take special care with Gliclazide 30 mg Prolonged-release tablets

This medicine should only be taken if you have regular food intake otherwise you may develop a low blood sugar (also known as “hypoglycaemia” or a “hypo”).
- Symptoms of a low blood sugar level (hypoglycaemia) include sweating, shaking, paleness, hunger, headache, irregular or fast heart beat, blurred vision, irritability, forgetfulness and confusion.
- If you have a “hypo” then take glucose tablets or a sugary drink followed by biscuits, a sandwich or your next meal (if due).
- In most cases of a “hypo”, symptoms will resolve if you consume sugar in a drink or food.
- Seek medical help if taking sugar does not resolve the symptoms.
- Severe cases of a “hypo” may develop confusion and unconsciousness. Never put anything in the mouth of an unconscious person. Seek medical help urgently.
- Some people, especially the elderly or those with hormone disorders, may not get symptoms of a “hypo” so that they may not be aware that their blood sugar is too low.
- If you are about to undergo an operation or have a serious injury or have an infection, your doctor may change you to insulin therapy temporarily.

Lowering of the haemoglobin level and breakdown of red blood cells (haemolytic anaemia) can occur in patients missing the enzyme glucose-6-phosphate dehydrogenase.

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

Some medicines may influence the effectiveness and safety of Gliclazide 30 mg Prolonged-release tablets if taken at the same time. Conversely, other medicines may be affected if they are taken at the same time as Gliclazide 30 mg Prolonged-release tablets.

The blood sugar lowering effect of glarglate may be strengthened and signs of low blood sugar levels may occur when taking one of the following medicines:
- Pain killers or antiinflammatories, such as ibuprofen or phenylbutazone,
- Medicines containing alcohol,
- Other medicines used to treat high blood sugar (oral antidiabetics) or insulin,
- Medicines to treat high blood pressure or heart failure (beta blockers, ACE inhibitors such as captopril or enalapril),
- Medicines to treat fungal infections (fluconazole),
- Medicines to treat indigestion and ulcers in the stomach or duodenum (H₂ receptor antagonists, such as ranitidine),
- Medicines to treat depression (monoamine oxidase inhibitors)
- Antibacterial medicines (e.g. sulphonamides).

The blood glucose lowering effect of glarglate may be weakened and raised blood sugar levels may occur when taking one of the following medicines:
- Medicine to treat breast disorders, heavy menstrual bleeding and endometriosis (danazol),
- Medicine to treat disorders of the central nervous system (chlorpromazine),
- Medicines inhibiting inflammation (glucocorticoids),
- Medicines to treat asthma (salbutamol, terbutaline when given by injection),
- Medicines used during labour (ritodrine given by injection).

Gliclazide may potentiate anticoagulation during concurrent treatment with warfarin (a medicine that inhibits blood clotting).

Consult your doctor before you start another medicinal product. If you go into hospital tell the medical staff you are taking Gliclazide 30 mg Prolonged-release tablets.

Taking Gliclazide 30 mg Prolonged-release tablets with food and drink
You may take Gliclazide 30 mg Prolonged-release tablets with food preferably at breakfast time. It is recommended that you do not drink alcohol during treatment with Gliclazide 30 mg Prolonged-release tablets.
Pregnancy and Breast-feeding

Pregnancy
Gliclazide 30 mg Prolonged-release tablets are not recommended for use during pregnancy. If you are planning to become pregnant or if you become pregnant tell your doctor.

Breast-feeding
Gliclazide 30 mg Prolonged-release tablets should not be taken if you are breast-feeding.

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

Driving and using machines
If your blood glucose levels become too low, then this could affect your concentration and therefore your ability to perform these tasks.

Children and adolescents (under 18 years of age)
Gliclazide 30 mg Prolonged-release tablets should not be used for the treatment of children and adolescents.

3. HOW TO TAKE GLICLAZIDE 30 MG PROLONGED-RELEASE TABLETS

Always take Gliclazide 30 mg Prolonged-release tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You should swallow your tablet(s) whole with breakfast (preferably the same time each day).

The usual once daily dose can vary from one to four tablets.
- The recommended starting dose is 30 mg daily.
- If necessary your doctor may increase the dose up to 60 mg, 90 mg or 120 mg per day.

If you have the impression that the effect of this medicine is either too strong or too weak, talk to your doctor or pharmacist.

Gliclazide 30 mg Prolonged-release tablets can be used to replace other oral antidiabetic medicine, exactly like your doctor has told you. If a combination therapy of Gliclazide 30 mg Prolonged-release tablets with other oral antidiabetic agents or insulin is initiated your doctor will determine the proper dose of each medicine individually for you.

People at risk of hypoglycaemia
You are at especial risk of hypoglycaemia (a “hypo”, see section 2) if:
- you skip meals or have irregular meals
- you are under-nourished
- you have hormone imbalance (endocrine disorders) or if you have recently stopped steroid therapy.

If you lie in these categories or have any other reason to be more at risk of a “hypo” then the minimum dose of 30 mg Gliclazide Prolonged-release tablets is recommended.
If you take more Gliclazide 30 mg Prolonged-release tablets than you should
If you have taken more Gliclazide 30 mg Prolonged-release tablets than you should, then your blood sugar may fall too low (hypoglycaemia or a “hypo”) and you may show signs of a “hypo” (see section 2). You should consume sugar and even seek medical advice.

Be aware that the state of hypoglycaemia may persist for some time. Severe cases of hypoglycaemia accompanied by altered behaviour or loss of consciousness require immediate treatment and admission to hospital. Ensure that you have a friend or colleague who knows about your condition and knows when to seek medical advice.

If you forget to take Gliclazide 30 mg Prolonged-release tablets
Do not take a double dose to make up for a forgotten tablet. Take the next dose as usual.

If you stop taking Gliclazide 30 mg Prolonged-release tablets
If you stop taking Gliclazide 30 mg Prolonged-release tablets then you should be aware that your blood sugar control will deteriorate. Do not stop taking Gliclazide 30 mg Prolonged-release unless told to do so by your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Gliclazide 30 mg Prolonged-release tablets can cause side effects, although not everybody gets them.

Hypoglycaemia or a “hypo” is an important and common side effect (affecting less than 1 person in 10) and will require immediate action if you experience it (take a sugary drink or sugary food). The symptoms include sweating, paleness, hunger, shaking, headache, irregular or fast heart beat, blurred vision, irritability, forgetfulness and confusion.

If the hypoglycaemia is severe or prolonged even after intake of sugar, you should stop taking Gliclazide 30 mg Prolonged-release tablets and should seek immediate medical attention. If not treated it could lead to drowsiness, loss of consciousness or possible coma.

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

Uncommon (affecting less than 1 person in 100):
- abdominal pain, nausea, vomiting, indigestion, diarrhoea and constipation

Rare (affecting less than 1 person in 1,000):
- skin rashes and itching, redness, hives, blistering
- changes in your blood (such as decrease in the number of certain cells in the blood which may cause paleness, prolonged bleeding, bruising, sore throat and fever)
- changes in your liver (which can cause yellow skin and eyes). These tend to disappear when the medicine is stopped.
- Your vision may be affected for a short time especially when the treatment starts. This is due to changes in the blood sugar level.

With other medicines of the same class (sulphonylureas), cases of severe changes in the number of blood cells and allergic inflammation of the wall of blood vessels have been described.
If any of the side effects gets serious, or if you notice any other side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE GLICLAZIDE 30 MG PROLONGED-RELEASE TABLETS**

- Keep out of the reach and sight of children.
- Store below 30 °C.
- Blister: Store in the original package in order to protect from moisture.
- Bottle: Keep the bottle tightly closed in order to protect from moisture.

Do not use Gliclazide 30 mg Prolonged-release tablets after the expiry date which is stated on the packet after EXP. The expiry date refers to the last day of that month.

The shelf life after first opening of the bottle is 60 days.

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 Gliclazide 30 mg Prolonged-release tablets contain**
- The active substance is gliclazide. Each tablet contains 30 mg of gliclazide.
- The other ingredients are:
  - hypromellose
  - stearic acid
  - silica, colloidal anhydrous.

**What Gliclazide 30 mg Prolonged-release tablets look like and contents of the pack**
Each tablet is white to off-white, capsule shaped tablets, engraved ‘APO 30’ on one side, plain on the other side.

The tablets are available in blisters of 7, 28, 30, 56, 60, 90, 95, 175 or 180 tablets and bottles of 100, 150, 200, 250 or 300 tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder:**  
[To be completed nationally]

**Manufacturer:**  
[To be completed nationally]

< Distributor: [to be completed nationally]>

**This leaflet was last approved in** {MM/YYYY}.
Module 4
Labelling

**Carton**

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARTON BOX</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Gliclazide 30 mg Prolonged-release tablets
Gliclazide

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 30 mg of gliclazide.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**

| 7 tablets: |
| 28 tablets: |
| 35 tablets: |
| 56 tablets: |
| 60 tablets: |
| 90 tablets: |
| 95 tablets: |
| 120 tablets: |
| 150 tablets: |
| 175 tablets: |
| 180 tablets: |
| 200 tablets: |
| 230 tablets: |
| 250 tablets: |
| 300 tablets: |
| 500 tablets: |

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.
Swallow whole. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP.:
9. **SPECIAL STORAGE CONDITIONS**

Store below 30 °C.

(Blister:)
Store in the original package in order to protect from moisture.

(Bottle:)
Keep the bottle tightly closed in order to protect from moisture. The shelf life after first opening of the bottle is 60 days.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

-Distributor: [to be completed nationally]-

12. **MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Gliclazide 30 mg

**Blister**

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Gliclazide 30 mg Prolonged-release tablets
Gliclazide

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

[To be completed nationally]

3. **EXPIRY DATE**

EXP.: 

4. **BATCH NUMBER**

Lot:

5. **OTHER**
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
HDPE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT
Gliclazide 30 mg Prolonged release tablets
Gliclazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains 30 mg of gliclazide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
100 tablets:
150 tablets:
200 tablets:
250 tablets:
300 tablets:

5. METHOD AND ROUTE(S) OF ADMINISTRATION
For oral use.
Swallow whole. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP:

9. SPECIAL STORAGE CONDITIONS
Store below 30 °C.

Keep the bottle tightly closed in order to protect from moisture. The shelf life after first opening of the bottle is 60 days.

<Opening date:>
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

Distributor: [to be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
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 Dizalid 30mg Prolonged Release Tablets, for the management of non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose, is approvable.

This application is submitted under Article 10(1) of Directive 2001/83, as amended. Dizalid 30mg Prolonged Release Tablets, has been shown to be a generic medicinal product of Diamicron® MR 30mg Tablets (PL 05815/0019) which was granted to Servier Laboratories Ltd. in the UK on 7th December 2000. The reference medicinal product authorised for not less than 10 years is Diamicron® 80mg tablets by Servier Laboratoires Limited, UK licensed in the UK since 21st December 1979 (UK PL 00093/0024).

Gliclazide is a well-known sulphonylurea given by mouth to lower blood glucose concentration in the treatment of type 2 diabetes mellitus. Gliclazide is used when dietary measures, weight loss and physical exercise are not enough to manage blood sugar concentrations in people with type 2 diabetes. Gliclazide acts by promoting insulin production. Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment. In addition to these metabolic properties, gliclazide has haemovascular properties.

The application is in accordance with Article 10(1) of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

A formal Environment Assessment was not submitted. This is acceptable as no increase in environmental risk is to be expected compared to that of the reference product.

No Risk Management Plan other than documentation of pharmacovigilance system has been provided. For generics this is generally acceptable if the innovator product is not subject to specific risk management measures, which is not the case for gliclazide.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provided 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.

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

Since a literature review has been presented for the Non-clinical Overview, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.
No new clinical study was submitted. The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Dizalid 30mg Prolonged Release Tablets |
| Name(s) of the active substance(s) (INN)         | Gliclazide                           |
| Pharmacotherapeutic classification (ATC code)   | Sulphonamides, urea derivatives      |
| Pharmaceutical form and strength(s)            | 30mg modified-release tablets        |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1823/001/DC                  |
| Reference Member State                         | United Kingdom                       |
| Member States concerned                        | Denmark                              |
| Marketing Authorisation Number(s)              | PL 20254/0013                        |
| Name and address of the authorisation holder    | Orifarm Generics A/S                 |
|                                               | Energivej 15, 5260 Odense S, Denmark  |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

3.2.S.1.1 Nomenclature

INN Name: Gliclazide

Chemical Names: N-[(hexahydrocyclopenta[c]pyrrol-2(1H)-ylamino)carbonyl]-4-methylbenzenesulfonamide

CAS Registry No: 21187-98-4

3.2.S.1.2 Structure

Structural formula:

![Structural formula]

Molecular formula: C_{15}H_{21}N_{3}O_{3}S

Molecular weight: 323.4

3.2.S.1.3 General Properties

Gliclazide is a white to almost white crystalline powder, sparingly soluble in acetone, slightly soluble in alcohol and freely soluble in methylene dichloride.

Melting point: 180 - 182 °C

Isomerism: Gliclazide does not exhibit isomerism.

Polymorphism: Not polymorphism known in the literature.

Manufacture

All aspects of the manufacture and control of gliclazide are supported by European Directorate for the Quality of medicines and Healthcare (EDQM) Certificates of Suitability from both active substance manufacturers. This certificate is accepted as confirmation of the suitability of gliclazide for inclusion in the medicinal product.

The active substance, gliclazide, is controlled by the Ph Eur monograph.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.
Gliclazide is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Certificates of Analysis for three batches of the active substance have been provided by both active substance manufacturers and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Satisfactory Certificates of Analysis have been provided for all aspects of the container-closure system working standards used by the active substance manufacturer and finished product manufacturer during validation studies. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff. Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely hypromellose, stearic acid and silica, colloidal anhydrous. All excipients comply with their relevant Ph Eur monographs with the exception of hypromellose which complies with the US Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients. An appropriate justification for the inclusion of each excipient has been provided.

None of the excipients used contain material of animal or human origin.

**Pharmaceutical Development**

The aim of formulation development was to develop a modified release tablet obtaining a product which is bioequivalent to the reference product Diamicron 80 mg tablets (Servier Laboratories Ltd).

**Dissolution and Impurity profiles**

Dissolution and impurity profiles of the drug product were found to be similar to that of the reference product.

**Manufacture**

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

**Manufacturing process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. In-process controls are appropriate considering the nature of the product and the method of manufacture. The manufacturing process has been validated on three pilot-scale batches and has shown satisfactory results.

**Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.
Container Closure System
The product is packaged either in blisters composed of polyvinylchloride/polyvinylidenechloride/aluminium (PVC/PVdC/Al) or high density polyethylene (HDPE) bottles with polypropylene caps. Specifications and a Certificate of Analysis for the package types used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in blister packs of 7, 28, 30, 56, 60, 90, 95, 175 or 180 tablets or in HDPE bottle packs of 100, 150, 200, 250 or 300 tablets. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 1 year has been set (reduced to 60 days shelf life after first opening), which is satisfactory. The precautions “Store below 30°C” is considered acceptable.

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

MAA form
The MAA form is pharmaceutically acceptable.

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

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

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of gliclazide are well known. As gliclazide is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview was written by a suitably qualified person. The report refers to 35 publications up to year 2007.

An acceptable justification for the absence of an environmental risk assessment has been provided.

III.3 CLINICAL ASPECTS
Clinical study reports
To support the application, the applicant has submitted three of bioequivalence studies. The conducted studies are appropriate for the applied product with respect to the modified release pharmaceutical form
GCP Aspects
A signed statement is submitted to confirm that the bioequivalence studies were carried out in accordance with regulations of the Institutional Review Board.

Biowaiver
Not applicable

Pharmacokinetic studies
Fasting study

Study title
Comparative, Randomized, 3-way Crossover Bioavailability Study of Gliclazide Modified-Release Tablets, Diamicron® MR Tablets (Servier Laboratories Ltd.), (UK) and Diamicron® MR Tablets (Servier Laboratories (AUST) Pty. Ltd.), (Australia) Under Fasting Conditions.

This study involved exposure to an Australian reference product as well as the product under test and the EU reference product. For the purposes of this report, only reference to the EU product and test product will be made.

Study design
Double-blinded, single-dose, standard randomized 3-way crossover relative bioavailability study performed on healthy adult male subjects under fasting conditions.

A complete protocol is submitted.

Pre-defined bioequivalence acceptance criteria
The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and Cmax. This is satisfactory.

Test Product
Name and strength: Gliclazide Modified-Release Tablets, 30 mg

Reference Product
Name and strength: Diamicron® MR Tablets (Servier Laboratories Ltd.), (UK)
Acceptability criteria: the reference product is marketed in the UK, an EU country and is therefore acceptable.

Subjects:
Healthy male subjects were fasted according to a standard protocol prior to dosing.

Dose administered:
Test: 30mg. Reference: 30mg.
Blood was taken prior to dosing (0) and then up to 72hours post dose.

The duration of sampling following dosing is sufficient for AUCt > 80% of AUCinf. The sampling frequency around Tmax is adequate to estimate Cmax.

Analysis of samples.
Samples were analysed using a validated LC-MS/MS method. This is acceptable.

Data was log-transformed. ANOVA was used for AUC and Cmax
Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (mean ± CV%)</th>
<th>Reference (mean ± CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>986.7 ± 22</td>
<td>1051.7 ± 24</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt; (ng.h/mL)</td>
<td>27249.1 ± 26</td>
<td>28028.7 ± 24</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>11 ± 32</td>
<td>9.51 ± 23</td>
</tr>
</tbody>
</table>

The measured pharmacokinetic parameters are consistent with those of the originator.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (median ± CV%)</th>
<th>Reference (median ± CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>94.0 (85.5 – 103.3)</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;T&lt;/sub&gt; (ng.h/mL)</td>
<td>96.9 (91.1 – 103.2)</td>
<td></td>
</tr>
</tbody>
</table>

The 90% confidence intervals for test/reference lie within the 80 – 125 acceptance criteria

The results presented are consistent with the demonstration of bioequivalence between the test and reference products in a fasted study.

**Fed study**

**Study title**
Comparative, Randomized, 3-way Crossover Bioavailability Study of Gliclazide Modified-Release Tablets, Diamicron® MR Tablets (Servier Laboratories Ltd.), (UK) and Diamicron® MR Tablets (Servier Laboratories (AUST) Pty. Ltd.), (Australia) Under Fed Conditions.

This study involved exposure to an Australian reference product as well as the product under test and the EU reference product. For the purposes of this report, only reference to the EU product and test product will be made.

**Study design**
Double-blinded, single-dose, standard randomized 3-way crossover relative bioavailability study performed on healthy adult male subjects under fed conditions.

A complete protocol is submitted.

**Pre-defined bioequivalence acceptance criteria**
The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and Cmax. This is satisfactory.

**Test Product**
Name and strength: Gliclazide Modified-Release Tablets, 30 mg

**Reference Product**
Name and strength: Diamicron® MR Tablets (Servier Laboratories Ltd.), (UK)
Acceptability criteria: the reference product is marketed in the UK, an EU country and is therefore acceptable.
Refer to Quality Assessment Report for information on batch sizes and biopharmaceutical assessment.

**Subjects:**
Healthy male subjects were dosed in the study.

Subjects were served a standard breakfast 30 mins before dosing according to a standard protocol.

**Dose administered:** Test: 30mg. Reference: 30mg.
Blood was taken prior to dosing and then up to 72 hours post dose.

The duration of sampling following dosing is sufficient for AUCt > 80% of AU Cinf. The sampling frequency around Tmax is adequate to estimate Cmax.

**Analysis of samples.**
Samples were analysed using a validated LC-MS/MS method.

Data was log-transformed. ANOVA was used for AUC and Cmax

**Results for main pharmacokinetic parameters:**

<table>
<thead>
<tr>
<th></th>
<th>Test (mean ± CV%)</th>
<th>Reference (mean ± CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>1180.3 ± 28</td>
<td>1276.2 ± 21</td>
</tr>
<tr>
<td>AUCt (ng.h/mL)</td>
<td>30923.6 ± 37</td>
<td>30624.5 ± 33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Test (median ± CV%)</th>
<th>Reference (median ± CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>10 ± 22</td>
<td>8 ± 19</td>
</tr>
</tbody>
</table>

The measured pharmacokinetic parameters are consistent with those of the originator.

**Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>90.7 (85.9 – 95.8)</td>
</tr>
<tr>
<td>AUCt (ng.h/mL)</td>
<td>99.3 (96.2 – 102.4)</td>
</tr>
</tbody>
</table>

The 90% confidence intervals for test/reference lie within the 80 – 125 acceptance criteria

The results presented are consistent with the demonstration of bioequivalence between the test and reference products in a fed study.

**Steady state study**

**Study title**
A Comparative, Randomized, Fasting Relative Bioavailability, Multiple-Dose, Steady-State, Two-Way Crossover, Blinded Study of a Test Tablet Formulation of Gliclazide Modified Release (30 mg), and an Equivalent Dose of a Commercially Available Reference Drug Product (Diamicron® MR, Servier, UK) in Fasted, Healthy, Adult Subjects.

**Study design:**
Double-blinded, multiple-dose, standard randomized 2-way crossover relative bioavailability study performed on healthy adult male and female subjects under fasting conditions.
The study design is acceptable. A study protocol is submitted.

**GCP certification**
A signed statement is submitted to confirm that Bioequivalence Studies were done in accordance with the regulations.

**Test Product**
Name and strength: Gliclazide Modified-Release Tablets, 30 mg

**Reference Product**
Name and strength Diamicron® MR Tablets, 30mg (Servier Laboratories Ltd.), (UK)
Acceptability criteria: The reference product is marketed in the UK, an EU country. This is acceptable.

**Subjects**
Healthy volunteers were dosed in the study.

**Dose administered:** Test: 30mg. Reference: 30mg. Subject received daily oral doses of 30 mg for 6 days.

**Pre-defined bioequivalence acceptance criteria**
The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and Cmax. This is satisfactory.

Blood samples were drawn prior to dosing time and up to 144 hours after the first dose of each period.

The duration of sampling following dosing is sufficient for AUCt > 80% of AUCinf. The sampling frequency around Tmax is adequate to estimate Cmax.

**Washout period**
The study took place over 20 days and included a washout period of 9 days between treatments. This is acceptable to avoid carryover.

Data was log-transformed. ANOVA was used for AUC and Cmax

Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th></th>
<th>Test (mean ± CV%)</th>
<th>Reference (mean ± CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>1304.5 ± 42</td>
<td>1345.8 ± 42</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>434 ± 76</td>
<td>429 ± 69</td>
</tr>
<tr>
<td>AUCt (ng.h/mL)</td>
<td>21627.7 ± 50</td>
<td>21512.3 ± 50</td>
</tr>
<tr>
<td></td>
<td>Test (median ± CV%)</td>
<td>Reference (median ± CV%)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>10 ± 34</td>
<td>7 ± 28</td>
</tr>
</tbody>
</table>

The measured pharmacokinetic parameters are consistent with those of the originator.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:
The 90% confidence intervals for test/reference lie within the 80 – 125 acceptance criteria

The results presented are consistent with the demonstration of bioequivalence between the test and reference products in a steady-state study.

**Analysis of samples.**
Samples were analysed using a validated LC-MS/MS method.

*Pharmacokinetic conclusion*
Based on the submitted bioequivalence studies, Gliclazide MR 30mg tablets are considered bioequivalent with Diamicron MR 30mg tablets.

*Pharmacodynamic studies*
New data are neither submitted nor required

**Expert Report**
The clinical overview refers to 19 references between 1991 and 2004. The clinical overview summaries the clinical efficacy and safety of gliclazide and provides a summary of the applicant’s bioequivalence studies. The clinical overview is acceptable.

**Post marketing experience**
No post-marketing data is available. The medicinal product has not been marketed in any country.

**Benefit-Risk assessment**
The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are pharmaceutically acceptable.

**MAA form**
The MAA form is pharmaceutically acceptable.

**CONCLUSIONS**
The efficacy and safety of the product is satisfactory for the grant of a product licence.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Dizalid 30mg Prolonged Release Tablets is well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Dizalid 30mg Prolonged Release Tablets and Diamicron® MR 30mg Tablets (Servier Laboratories Ltd.), (UK)
No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with that for 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 gliclazide 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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>