HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

**TRANSPARENCY COMMITTEE**

OPINION

27 April 2011

Review of the dossier for proprietary medicinal products included for a period of five years by the order of 20 December 2004 (*Journal Officiel* of 28 December 2004)

**GLUCOVANCE 500 mg/2.5 mg, film-coated tablets**
**B/30 (CIP code: 358 016-2)**

**GLUCOVANCE 500 mg/5 mg, film-coated tablets**
**B/30 (CIP code: 358 028-0)**

**Applicant: MERCK SERONO**

metformin hydrochloride / glibenclamide
ATC code: A10BD02

List I

Joint renewal of the following proprietary medicinal products:

**GLUCOVANCE 500 mg/2.5 mg, film-coated tablets**
**B/90 (CIP code: 358 022-2)**

**GLUCOVANCE 500 mg/5 mg, film-coated tablets**
**B/90 (CIP code: 358 033-4)**

Date of initial Marketing Authorisation (mutual recognition procedure): 18 October 2001

Reason for the request: Renewal of inclusion on the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

# 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

## 1.1. Active ingredients

metformin hydrochloride / glibenclamide

## 1.2. Indication

"Treatment of type 2 diabetes in adults, as replacement for combination therapy with metformin and glibenclamide, in patients whose blood glucose is stable and well-controlled."

## 1.3. Dosage[1]

"Oral route. For use in adults only

**General**

*GLUCOVANCE 500 mg/2.5 mg*

As with any antidiabetic agent, the dosage should be adjusted according to individual metabolic response (blood glucose, $HbA_{1c}$).

*GLUCOVANCE 500 mg/5 mg*

As with any antidiabetic agent, the dosage should be adjusted according to individual metabolic response (blood glucose, $HbA_{1c}$).
GLUCOVANCE 500 mg/5 mg should preferably be used in patients insufficiently controlled with GLUCOVANCE 500 mg/2.5 mg.

**Starting treatment:**

Treatment should be started with the fixed-dose combination that corresponds to the doses of metformin and glibenclamide originally prescribed. The dosage should then be gradually increased, if necessary, in accordance with laboratory test results.

**Dosage adjustment**

The dosage should be adjusted every two weeks or longer, in one-tablet steps, according to blood glucose values.
A gradual increase in dosage may improve gastrointestinal side effects and avoid hypoglycaemia.

**Maximum recommended dosage:**

*GLUCOVANCE 500 mg/2.5 mg*

The maximum recommended dosage is six tablets of GLUCOVANCE 500 mg/2.5 mg a day.

*GLUCOVANCE 500 mg/5 mg*

The maximum recommended dosage is three tablets of GLUCOVANCE 500 mg/5 mg a day.
Exceptionally, a dosage of four tablets of GLUCOVANCE 500 mg/5 mg may be needed.

**Distribution of dosages:**

*GLUCOVANCE 500 mg/2.5 mg*

Doses should be distributed according to the daily dose for a given patient, i.e.:

- 1 dose a day: in the morning with breakfast for a dosage of 1 tablet/day;

[1] usual dosage of glibenclamide: the recommended initial dose is half a 2.5 mg tablet a day, taken before breakfast. Dosage adjustments are usually made in half-tablet steps depending on glycaemic response, in divided doses taken before the two or three main meals. As maintenance therapy, the maximum dosage is 15 mg a day.
usual dosage of metformin: the usual starting dosage when combined with other oral antidiabetic agents is one tablet of GLUCOPHAGE 500 mg or 850 mg 2 or 3 times daily given during or after meals.
After 10 to 15 days the dosage should be adjusted on the basis of blood glucose measurements.
In patients taking a high dose of metformin (2-3 g/day), two GLUCOPHAGE 500 mg tablets may be replaced by one GLUCOPHAGE 1000 mg tablet.
The maximum recommended dose of metformin is 3 g/day.

- 2 doses a day: in the morning and evening, for a dose of 2 or 4 tablets/day;
- 3 doses a day: morning, midday and evening, for a dose of 3, 5 or 6 tablets/day;

Tablets should be taken with meals. The distribution of doses should be adjusted according to each patient's normal mealtimes. However, all doses of tablets should be followed by a meal containing sufficient carbohydrate to avoid onset of hypoglycaemia.

*GLUCOVANCE 500 mg/5 mg*
Doses should be distributed according to the daily dosage for a given patient, i.e.:
- 1 dose a day: in the morning with breakfast for a dosage of 1 tablet/day;
- 2 doses a day: in the morning and evening, for a dosage of 2 or 4 tablets/day;
- 3 doses a day: morning, midday and evening, for a dosage of 3 tablets/day.

Tablets should be taken with meals. The distribution of doses should be adjusted according to each patient's normal mealtimes. However, all doses of tablets should be followed by a meal containing sufficient carbohydrate to avoid onset of hypoglycaemia.

**Combination with insulin therapy:**
No clinical data are available on combination with insulin.

**Elderly patients:**
The dosage of GLUCOVANCE should be adjusted according to renal function (start with one tablet of GLUCOVANCE 500 mg/2.5 mg). Renal function should be monitored regularly.

**Use in children:**
GLUCOVANCE is not recommended in children."

### 1.4. Contraindications
"- Hypersensitivity to the active substances or to any of the excipients
- Type 1 diabetes, ketoacidosis, or diabetic pre-coma
- Renal failure or impaired renal function (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
- Acute or chronic disease which may cause tissue hypoxaemia, such as:
  - heart or respiratory failure
  - recent myocardial infarction
  - shock.
- Hepatocellular failure
- Acute alcohol intoxication, alcoholism
- Lactation
- Concomitant use of miconazole."

### 1.5. Special warnings and precautions for use (see SPC)

"Renal insufficiency

Metformin is mainly excreted in the urine. Metformin-related lactic acidosis increases with the degree of impairment of renal function, therefore, serum creatinine concentrations should be determined regularly:

- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Hypoglycaemia

As GLUCOVANCE contains an antidiabetic sulfonylurea, it exposes the patient to risk of episodes of hypoglycaemia. After treatment has been initiated, increasing the dosage gradually may avoid onset of hypoglycaemia.

This product should only be prescribed if the patient is likely to eat regularly (including breakfast). It is important that carbohydrates are eaten regularly, as the risk of hypoglycaemia is increased by delaying a meal, not eating enough or by a meal with the wrong proportion of carbohydrates. Hypoglycaemia occurs most often during low-calorie diets, after major or prolonged effort, after ingestion of alcohol, or during concomitant use of other antidiabetic medicines."

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification (2010)

| | |
|---|---|
| A: | Alimentary tract and metabolism |
| A10: | Drugs used in diabetes |
| A10B: | Blood glucose lowering drugs, excluding insulins |
| A10BD: | Combinations of oral blood glucose lowering drugs |
| A10BD02: | metformin and sulfonamides |

### 2.2. Medicinal products in the same therapeutic category

Comparator medicines

- proprietary medicinal products containing metformin and generic versions of these:

GLUCOPHAGE 500 mg, 850 mg, 1 000 mg, tablets, indicated for the treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control in adults (as monotherapy or in combination with other oral antidiabetic agents), in children from 10 years of age and adolescents (as monotherapy or in combination with insulin).

Fewer diabetes-related complications were observed in overweight adult type 2 diabetics treated with metformin as first-line therapy, after failure of dietary measures.

- proprietary medicinal products containing glibenclamide and generic versions of these:

DAONIL 5 mg and SEMI DAONIL 2.5 mg, scored tablets, are indicated in combination with a suitable diet for the treatment of patients with non-insulin dependent diabetes, in patients who respond inadequately to dietary measures alone.

### 2.3. Medicines with a similar therapeutic aim

These are proprietary medicinal products indicated as dual oral therapy, in combination with metformin, in patients with type 2 diabetes with insufficient glycaemic control despite maximal tolerated dose with oral metformin monotherapy:

- Other antidiabetic sulfonylureas
- Glitazone
- Alpha-glucosidase inhibitors
- Glinide
- DPP-4 inhibitors (gliptins)
- Incretin mimetics by injection

## 3 SUMMARY OF PREVIOUS TRANSPARENCY COMMITTEE OPINIONS

Committee Opinion of 16 June 2004

Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use

The efficacy/adverse effects ratio of this proprietary medicinal product is high.
The actual benefit is substantial.
GLUCOVANCE does not provide any improvement in actual benefit (IAB) in terms of efficacy or tolerance compared with the combination of glibenclamide and metformin given separately (IAB V).

At the time the Committee had access to two randomised double-blind controlled trials designed to evaluate the efficacy (measured by reduction in HbA1c) and tolerance after 16 weeks of treatment of GLUCOVANCE medicinal products compared with the use of each of the active ingredients taken separately, in patients not controlled by dietary measures, physical exercise and monotherapy with metformin or an antidiabetic sulfonylurea. The Committee concluded that the fixed-dose combination was more effective than each of the constituents used as monotherapy.

Committee Opinion of 5 October 2005

Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use of packs of 90 tablets

The actual benefit is substantial.
No IAB (IAB V) compared with existing presentations.

## 4 ANALYSIS OF DATA MADE AVAILABLE SINCE PREVIOUS OPINION

### 4.1. Efficacy data

As part of its dossier for renewal of its listing, the company submitted four new studies.

- One cohort study[2] to assess compliance with antidiabetic therapy for the fixed-dose combinations metformin + glibenclamide, metformin + rosiglitazone, and metformin + glipizide, in patients funded by the US mutual company Texas Medicaid. The study will not be described in this document as the data are not transposable (patient profiles different from those monitored in France, other forms of treatment, etc.).

- One study[3] assessed the efficacy and tolerance of the fixed-dose combination metformin + glibenclamide compared with those of free combinations of metformin + pioglitazone or sulfonylurea + pioglitazone. In this study the metformin dose in the fixed-dose combination was 400 mg. The results of this study will not be given here as this dose is not available in France.

- One study[4] compared the efficacy and tolerance of the fixed-dose combination metformin + glibenclamide with those of a free combination of metformin + rosiglitazone. The relevance of the comparator and doses administered in this study is debatable. The tolerance profile of rosiglitazone, particularly its cardiovascular tolerance profile, meant that its use was controversial at the time the study was carried out. It should be noted that Marketing Authorisations for proprietary medicinal products containing rosiglitazone have been suspended since 23 September 2010.
  The maximum doses permitted in the study were 2 000 mg of metformin / 10 mg of glibenclamide for the fixed-dose combination, divided into two doses a day, and 2 000 mg of metformin and 8 mg of rosiglitazone for the free combination. The study did not assess the presentations of GLUCOVANCE available in France in the fixed-dose combination, which make it impossible to administer this dosage. The study will therefore not be described.

- One observational study, the FREGATE study. The study was carried out between February 2007 March 2010 among general practitioners in non-hospital practice. The study included both retrospective and prospective (over 6 months) collection of follow-up data from a cohort of patients with type 2 diabetes treated for at least a month with a combination of metformin and glibenclamide, either in the form of a fixed-dose combination (GLUCOVANCE), or in an adjustable form. Its main aim was to study the treatment of these patients by general practitioners.
  The validity of the study's results was compromised by its exploratory design.
  The Committee was not able to use this study because of the lack of evidence of representativeness of the doctors and patients included in the study, the absence of adequate analysis of change in $HbA_{1c}$, the unusable results on compliance, and the lack of compliance with the indication of Marketing Authorisation and clinical practice guidelines.

[2] Cheong C, Barner JC, Lawson KA, Johnsrud MT. Patient adherence and reimbursement amount for antidiabetic fixed-dose combination products compared with dual therapy among Texas Medicaid recipients. Clin Ther. 2008; 30(10): 1893-907

[3] Comaschi M, Corsi A, Di Pietro C, Bellatreccia A, Mariz S; COM06 Study Investigators The effect of pioglitazone as add-on therapy to metformin or sulphonylurea compared to a fixed-dose combination of metformin and glibenclamide on diabetic dyslipidaemia. Nutr Metab Cardiovasc Dis. 2008; 18(5): 373-9

[4] Garber A., Klein E., Bruce S., Sankoh S., Mohideen P. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diab. Obes. Metabol., 2006, 8.2: 156-163

**4.2. Adverse effects**

Based on postmarketing pharmacovigilance data for GLUCOVANCE proprietary medicinal products obtained from the three most recent Periodic Safety Update Reports (PSUR nos. 12, 13 and 14) covering the period 01 August 2006 to 31 July 2009, 59 adverse effects were reported, 39 of which were considered to be serious.

There were six deaths (two not examined because of lack of information, two considered to be possibly related to treatment and two for which it was not possible to establish any causal relationship with GLUCOVANCE therapy due to insufficient information).

The cases reported included, in particular:

- Eleven serious cases of hypoglycaemia. In three cases, GLUCOVANCE was combined with other antidiabetics including one antidiabetic sulfonylurea (glibenclamide + metformin, pioglitazone + repaglinide + sitagliptin, glimepiride + insulin).
- Four cases of lactic acidosis, two of which were combined with renal failure and in which GLUCOVANCE was administered with other oral antidiabetics (metformin or rosiglitazone + glibenclamide).
- Two cases of acute pancreatitis (one associated with lactic acidosis and elevated triglycerides, one in which COMPETACT (combination of metformin + pioglitazone) was prescribed concomitantly with GLUCOVANCE).

These data demonstrate the onset of serious adverse effects related to concomitant administration of GLUCOVANCE with one of its constituents (metformin or glibenclamide) leading to either risk of metformin overdose and risk of lactic acidosis or risk of severe hypoglycaemia, particularly in elderly subjects or those with concomitant comorbidities (renal failure etc.), so confirming the risks associated with incorrect use of GLUCOVANCE proprietary medicinal products.

**4.3. Conclusion**

Since the last opinion delivered by the Committee, no other studies have been made available comparing GLUCOVANCE proprietary medicinal products with its two active ingredients taken separately or with other dual therapies. It is therefore difficult to determine the benefit of the fixed-dose combination.

The data provided referred to administration of low doses of metformin.

The combination of metformin + sulfonylurea is relevant in view of current guidelines. However,

- the choice of glibenclamide as sulfonylurea in the context of a fixed-dose combination is debatable because of the high risk of hypoglycaemia, particularly if metformin needs to be titrated;
- this fixed combination raises the issue of dosage adjustment. The metformin dose (1500 mg a day) recommended for GLUCOVANCE 500 mg / 5 mg is low compared with the doses assessed in the available studies, notably in the UKPDS study, which assessed the effects of metformin in terms of morbidity and mortality; in that study the mean daily dosage was 2 550 mg of metformin;
- The fixed-dose combination of GLUCOVANCE 500 mg / 5 mg restricts the clinical adjustment of metformin and is not relevant in patients treated with metformin doses > 1 500 mg, which in practice is often the case.

The main risk of misuse is prescription of the fixed-dose combination as first-line therapy, which does not comply with current clinical practice guidelines. It should be remembered that according to the guidelines, metformin should be used as monotherapy with the option of increasing doses up to 2 000 - 3 000 mg a day if blood glucose control is inadequate and if these doses are well tolerated, before another oral antidiabetic is added. The thrice-daily dose of metformin 500 mg in a fixed-dose combination is therefore not suitable for treating patients.

GLUCOVANCE 500 mg/2.5 mg given at a dosage of 4-6 tablets daily could be justified in terms of the metformin dosage, but this presentation exposes patients to increased risk of hypoglycaemia.

## 5 DATA ON THE USE OF THE MEDICINAL PRODUCT

According to IMS data (moving annual total May 2010), GLUCOVANCE proprietary medicinal products were the subject of 262 000 prescriptions at a mean daily dosage of 2.8 tablets.
The number of prescriptions was:

- 54 000 for GLUCOVANCE 500 mg / 2.5 mg in box of 30 tablets
- 52 000 for GLUCOVANCE 500 mg / 2.5 mg in box of 90 tablets
- 52 000 for GLUCOVANCE 500 mg / 5 mg in box of 30 tablets
- 105 000 for GLUCOVANCE 500 mg / 5 mg in box of 90 tablets.

## 6 TRANSPARENCY COMMITTEE CONCLUSIONS

### 6.1. Re-assessment of Actual Benefit for the proprietary medicinal products GLUCOVANCE 500 mg/2.5 mg and 500 mg/5 mg, film-coated tablets

Type 2 diabetes is a chronic disease with potentially serious complications, particularly cardiovascular complications.
The aim of GLUCOVANCE medicinal product is to treat hyperglycaemia.

Efficacy/adverse effects ratio:
In the absence of any relevant and specific new clinical data, it is not possible to evaluate the clinical benefit. In this regard, the benefit to patients of this fixed-dose combination of 500 mg of metformin and 2.5 or 5 mg of glibenclamide has not been established.
Glibenclamide is a sulfonylurea carrying a high risk of serious severe hypoglycaemia.
GLUCOVANCE proprietary medicinal products contain too low a dose of metformin and/or too high a dose of glibenclamide. With GLUCOVANCE 500 mg/5 mg, maintenance of an effective dose of 1 500 mg of metformin[5] is combined with a high dosage of glibenclamide (15 mg). The same is true for the proprietary medicinal product GLUCOVANCE 500 mg/2.5 mg. These proprietary medicinal products therefore expose patients to a substantial and potentially serious risk of hypoglycaemia, particularly in elderly diabetics and/or those at high risk of cardiovascular disease. For GLUCOVANCE 500 mg/5 mg the dose of metformin and that of glibenclamide in both formulations of GLUCOVANCE proprietary medicinal products are not suitable for treating patients.
It should be noted that new fixed-dose combinations do include a 1 000 mg metformin dose.

An efficacy/adverse effects ratio for GLUCOVANCE proprietary medicinal products cannot therefore be established.

[5] A higher dose could be beneficial and well-tolerated.

Place in the treatment strategy

The aims of treatment are control of blood glucose, i.e. control of $HbA_{1c}$ and control of concomitant risk factors.

According to the guideline 'Drug therapy in type 2 diabetes', published by the French Healthcare product Safety Agency (AFSSAPS) and HAS in November 2006, initial treatment for type 2 diabetes consists of assessment and realistic modification of lifestyle (diet and exercise). The adoption of an active lifestyle and diet planning are essential interventions at all stages of diabetes management.

Oral antidiabetics should be introduced when blood glucose is no longer adequately controlled ($HbA_{1c}$ > 6%) by dietary and lifestyle measures (DLM). There are four categories of oral antidiabetics: metformin, alpha-glucosidase inhibitors (AGI), insulin secretagogues and glitazone.

These guidelines, currently being updated, do not include five antidiabetic therapies which received a Marketing Authorisation after 2006, i.e. two GLP-1 analogues, exenatide (Marketing Authorisation November 2006) and liraglutide (Marketing Authorisation June 2009); and three DPP-4 inhibitors, sitagliptin (Marketing Authorisation March 2007), vildagliptin (Marketing Authorisation September 2007) and saxagliptin (Marketing Authorisation October 2009).

The different stages of treatment are summarised in the table below.

**Treatment strategy (LTC 8 - Type 2 Diabetes)[6]**

| **$HbA_{1c}$ levels** | **Treatment** | **Target $HbA_{1c}$** |
|---|---|---|
| $HbA_{1c}$ between 6% and 6.5% despite DLM | Metformin monotherapy (or AGI if metformin is poorly tolerated or contraindicated) | < 6.5 % |
| $HbA_{1c}$ > 6.5 % despite DLM | Metformin monotherapy or insulin secretagogue or AGI | Maintain $HbA_{1c}$ < 6.5% |
| $HbA_{1c}$ > 6.5 % despite monotherapy and DLM | Dual therapy* | Reduce $HbA_{1c}$ < 6.5% |
| $HbA_{1c}$ > 7% despite dual oral therapy and DLM | - Triple combination therapy: metformin + insulin secretagogue + glitazone<br>or<br>- insulin + metformin ± other OAD except glitazone | Reduce $HbA_{1c}$ < 7% |
| $HbA_{1c}$ > 8% despite triple therapy and DLM | - insulin + metformin ± other OAD except glitazone | Reduce $HbA_{1c}$ < 7% |

DLM: dietary and lifestyle measures; OAD: oral antidiabetics; AGI: alpha-glucosidase inhibitor

* metformin + insulin secretagogue (sulfonylurea or glinide), metformin + glitazone, metformin + alphaglucosidase inhibitor, insulin secretagogue + glitazone, or insulin secretagogue + alphaglucosidase inhibitor.

The most recent EASD (European Association for the Study of Diabetes) and ADA (American Diabetes Association) guidelines[7] have excluded glibenclamide from their treatment algorithm, as a sulfonylurea is not an indispensable part of the range of medicines available (there are other sulfonylureas with a lower risk in terms of hypoglycaemia).

So the role of GLUCOVANCE proprietary medicinal products in the treatment strategy is difficult to determine from the available evidence, but alternative medical products exist.

[6] Management of type 2 diabetes. Doctor's guide – Long-term condition (*ALD*), HAS – May 2006

[7] D. M. Nathan et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, volume 31, number 12, December 2008

In practice, it is better to be able to give each active ingredient separately so as to be able to adjust the dosage of each category of antidiabetic agent individually and according to blood glucose balance over time.

Public health benefit:
In view of the available data, no public health benefit is anticipated for the GLUCOVANCE range of proprietary medicinal products.

Conclusion:
For all these reasons, the Committee considers that the actual benefit of the GLUCOVANCE range of proprietary medicinal products is now insufficient for reimbursement by National health Insurance with regard to the available therapies.

**6.2. Improvement in actual benefit (IAB)**
Not applicable

**6.3. Therapeutic use**
Not applicable (see section 6.1.)

**6.4. Target population**
Not applicable

**6.5. Transparency Committee recommendations**
The Transparency Committee recommends removal from the list of medicines refundable by National Health Insurance in the indication and at the dosage in the Marketing Authorisation.