

**Direction de l'Évaluation  
Des Médicaments et des Produits Biologiques**

# **PAEDIATRIC PUBLIC ASSESSMENT REPORT EU Work Sharing Procedure – Assessment of Paediatric Data**

**GLUCOVANCE, film-coated tablet**  
500/2.5 mg and 500/5mg  
metformin+glibenclamide

**Applicant: MERCK SANTE S.A.S.**

<b>Date of the PaedPAR: June 2008</b>
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**Information about the initial procedure:**

<b>Rapporteur</b>	France
<b>Co-Rapporteur</b>	Netherlands
<b>Paediatric assessment report Procedure start date :</b>	October 24 <sup>th</sup> , 2005
<b>Deadline for (Co)-Rapporteur's preliminary report</b>	December 22 <sup>nd</sup> , 2005
<b>Clock-stop</b>	February 1 <sup>st</sup> , 2006.
<b>Deadline for Rapporteur's final report</b>	June 27 <sup>th</sup> , 2006
<b>Deadline for member states final comments</b>	July, 23 <sup>rd</sup> 2006
<b>End of procedure</b>	July 31 <sup>st</sup> , 2006

## **1. INTRODUCTION**

GLUCOVANCE film-coated tablets has been listed under the "EU worksharing project in the assessment of available paediatric data". Consequently, as a part of this procedure, the Marketing Authorisation Holder (MAH) has submitted the requested paediatric file for GLUCOVANCE 500/2.5 mg and 500/5 mg, film-coated tablets.

The procedure started on October 24<sup>th</sup>, 2005, France and The Netherlands having been appointed as Rapporteur and Co-Rapporteur, respectively.

This paediatric dossier consisted of the following documentation:

- a pharmacokinetic study: a single dose study designed to evaluate the pharmacokinetics, safety, and tolerability of Glucovance 250 mg/1.25 mg in children (aged 10 to 12 years old, N=8) and adolescents (aged 13 to 16 years old, N=20) with type 2 diabetes who were receiving stable doses of insulin;
- an efficacy and safety double-blind study and its open label extension designed to test the superiority of Glucovance (250/1.25 mg) to each of the monotherapies (metformin tablets 500 mg or glibenclamide capsules 2.5 mg) in paediatric patients 9-16 years old with type 2 diabetes mellitus not adequately controlled with diet and exercise alone, or diet and exercise with a single oral antihyperglycemic therapy.

Based on the dossier review, the paediatric clinical trial was considered not sufficient to justify a formal therapeutic indication in children. Nevertheless, some statements to be included in the current summary of product characteristics (SPC) were proposed regarding the product's use in children.

## About the product

Glucoavance is a fixed dose combination of metformin hydrochloride and glibenclamide.

Metformin is an oral antidiabetic drug belonging to the class of biguanides. It lowers both basal and postprandial plasma glucose levels. It does not stimulate insulin secretion and therefore does not produce by itself hypoglycaemic reactions. Although its mechanism of action is not yet fully characterised, there is general agreement that metformin acts mainly by decreasing hepatic glucose production. It may also increase insulin sensitivity, improving peripheral glucose uptake and utilisation in muscle and delay intestinal glucose absorption.

Glibenclamide (also known as glyburide) is an oral antidiabetic agent that belongs to the sulphonylurea (SU) class of drugs. The primary mode of action of glibenclamide involves the stimulation of insulin secretion from the pancreatic beta cells.

Glucoavance is indicated for the treatment of type 2 diabetes mellitus in adults, as replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled.

Glucoavance 500/2.5 mg and Glucoavance 500/5 mg are registered within the European Union through mutual recognition procedure with France acting as Reference Member State. Furthermore, the product is also approved through national procedures in seven European countries (Bulgaria, Cyprus, Czech Republic, Poland, Romania, Slovakia, and Slovenia).

In the United States three dose strengths are available (250/1.25 mg, 500/2.5 mg and 500/5 mg).

### **Background on type 2 diabetes in children and adolescents:**

Key elements of the pathophysiology of type 2 diabetes are resistance of peripheral tissues (mainly fat tissue, muscles and liver) to insulin (insulin resistance), and progressive loss of the functionality of beta-cells (i.e. the ability of beta-cells to adequately respond with insulin secretion and synthesis to glycaemic stimulus). Over hyperglycaemia develops when a defect in insulin action is no longer compensated by increased insulin secretion.

It is acknowledged that the pathogenesis of type 2 diabetes in children and adolescents is similar to that of the adults, with the same key features being present in both populations. Similarly, the clinical manifestations of type 2 diabetes in the paediatric population are similar to those in adults

Typically, the paediatric patients are diagnosed with type 2 diabetes in puberty, with the mean age ranging from 13 to 14 years in reported series. Coinciding with the increasing prevalence of obesity in children (particularly in the USA), the incidence of type 2 diabetes in children and adolescents has recently markedly increased.

#### *Treatment of type 2 diabetes in children:*

The first line therapy of type 2 diabetes in children and adults is lifestyle modification with diet and exercise. Indeed, it has been demonstrated that even a modest weight loss can markedly improve glycaemic control and insulin resistance. Moreover, lifestyle intervention with regular, moderate physical activity has been shown to improve insulin sensitivity in overweight children. Nevertheless, the implementation of lifestyle modifications may prove challenging in clinical practice, and usually require a multidisciplinary and individualised approach.

Among the oral antidiabetic agents, only metformin has been granted a specific therapeutic indication in patients under 15 years old: indeed, metformin can be used in children from 10 years of age and adolescents.

Due to its well established efficacy and safety profile, metformin is currently considered the standard first-line therapy for obese, insulin resistant paediatric patients with type 2 diabetes.

However, it is currently estimated that approximately 5% of type 2 diabetic children do not tolerate metformin due to gastrointestinal side-effects such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.

Moreover, type 2 diabetes being a progressive disease, addition of a second antidiabetic therapy may be needed after a certain length of time in case glycaemic control is no longer achieved.

The other type 2 diabetes treatment approved in children and adolescents is insulin.

At the time of diagnosis and depending on presentation, insulin therapy may be necessary, but with close medical follow-up, and it may be reduced, substituted, or even discontinued within a few weeks after glucose control is achieved. However, it is estimated that up to 30 to 50% of the adolescents will require insulin administration after two years of metformin therapy.

Although optimal glycaemic control can be obtained with insulin therapy, it often results in significant weight gain. Moreover, treatment adherence to daily injections is an issue, particularly in adolescents.

## **2. QUALITY ASPECTS**

NA

## **3. NON-CLINICAL ASPECTS**

NA

## **4. CLINICAL ASPECTS**

### **4.1 Introduction**

In the recent years, the European Community has supported effort to increase the submission of clinical studies conducted in children, based on data previously submitted to the Food and Drugs Administration (FDA) in the USA. The aim is to gain knowledge on the use of medicinal products in children and adolescents and to make these data available. Consequently, in this context, the MAH has submitted paediatric data for Glucovance to the European Union.

### **4.2 Pharmacokinetic (PK) aspects:**

The submitted dossier included one pharmacokinetic study. It was a single dose study designed to evaluate the pharmacokinetics, safety, and tolerability of Glucovance 250 mg/1.25 mg in children (ages: 10 to 12 years, N=8) and adolescents (ages: 13 to 16 years, N=20) with type 2 diabetes who were receiving stable doses of insulin.

28 subjects were enrolled, treated and completed the study.

Subjects were dosed five minutes prior to a standard breakfast preceded by a 10-hour overnight fast with a single tablet of Glucovance 250 mg/1.25 mg. At the same time, each subject's routine insulin dose was decreased by 50%.

#### *Results:*

For metformin, mean C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-4</sub> and t<sub>1/2</sub> differed by no more than 7% between children and adolescents. Median metformin T<sub>max</sub> was the same in the two age groups. Glibenclamide pharmacokinetics appeared to be similar in children and adolescents, with no more than a 10% difference in AUC<sub>0-t</sub> and AUC<sub>0-4</sub> between the two age groups. Although the mean C<sub>max</sub> of glibenclamide was 17% lower and the mean t<sub>1/2</sub> of glibenclamide was 25% greater in children than in adolescents, the variability of these two parameters was large.

Compared to historical data, C<sub>max</sub> and AUC values for metformin and glibenclamide are comparable between paediatric and adult patients. However, C<sub>max</sub> of glibenclamide was reached much faster in the

paediatric patients (median Tmax 1h) compared to adult patients (median Tmax 4.5h). The clinical relevance of such differences has not been established.

#### **Conclusion:**

The single dose PK study conducted in children and adolescents with type 2 diabetes showed that glibenclamide and metformin pharmacokinetics were comparable between children and adolescents patients. Based on historical data, C<sub>max</sub> and AUC values for metformin and glibenclamide are comparable between paediatric and adult patients. However, C<sub>max</sub> of glibenclamide was reached much faster in the paediatric patients (compared to adult patients) and the clinical relevance of such differences has not been established.

However, no further information can be drawn from this study.

More importantly, this study has been conducted with a dosage of Glucovance 250/1.25 mg) that is not approved within the EU.

Consequently, this study is of limited value with respect to the use of Glucovance in children and adolescents in the EU.

#### **4.3 Pharmacodynamic (PD) aspects:**

No additional data were provided in the paediatric dossier regarding clinical pharmacology.

#### **4.4 Efficacy and safety in the paediatric population**

Efficacy and safety data submitted by the Marketing Authorisation Holder consisted of a double-blind efficacy and safety study and its open-label extension.

In its initial 26-week period, the study was a multicenter, randomised, active-controlled, double-blind, three-arm, parallel-group clinical trial evaluating the safety and efficacy of Glucovance 250 mg/1.25 mg versus metformin and glibenclamide monotherapies in paediatric patients 9-16 years old with type 2 diabetes mellitus not adequately controlled with diet and exercise alone, or diet and exercise with a single oral antihyperglycemic therapy.

The maximum allowed dose for all subjects was 1500 mg metformin and 7.5 mg glibenclamide.

The primary efficacy variable was change in HbA<sub>1c</sub> from baseline to Week 26.

The study was designed to test the superiority of Glucovance (250/1.25 mg) to each of the monotherapies (metformin tablets 500 mg or glibenclamide capsules 2.5 mg).

The primary objective was to compare, after 26 weeks of oral administration of double-blind treatment, the mean change from baseline in HbA<sub>1c</sub> achieved with Glucovance 250 mg/1.25 mg therapy with the change from baseline in HbA<sub>1c</sub> achieved with metformin monotherapy.

The secondary objectives were to compare, after 26 weeks of oral administration of double-blind treatment, the mean change from baseline in HbA<sub>1c</sub> achieved with Glucovance 250 mg/1.25 mg therapy with the change from baseline in HbA<sub>1c</sub> achieved with glibenclamide, to assess the final mean HbA<sub>1c</sub>, and also to compare the mean changes from baseline in fasting glucose, fasting plasma insulin and body weight, and to ascertain the safety and tolerability of Glucovance 250 mg/1.25 mg.

In addition, an open-label extension for subjects who completed 26 weeks of double-blind treatment, who were discontinued from double-blind treatment due to lack of glycaemic control or who exceeded a mean fasting glucose (MFG) of 350 mg/dl after the lead-in phase was designed to assess the long-term safety and tolerability of Glucovance 250 mg/1.25 mg therapy.

#### **Summary of efficacy results:**

167 patients with type 2 diabetes, ages 0-16, were randomised and received double-blind medication for 26 weeks.

The Intent To Treat (ITT) population consisted of the 160 subjects who had HbA1c measurements at baseline and endpoint.

87 (52%) patients had never previously received any antidiabetic medication. Previous antihyperglycaemic medication consisted mainly of metformin (56; 33.5%), insulin (24; 14%) or a sulfonylurea (SU) (10; 6%).

- **Efficacy results from the double-blind phase:**

Results regarding the primary endpoint (HbA1c) and the final dose of treatment therapy received are summarised in Table 1

**Table 1. Mean change in HbA1c during the double-blind period**

HbA1c	Glucovance N=57	Metformin N=54	Glibenclamide N=49
Baseline	7.85	7.99	7.70
Week 26/last	7.05	7.46	6.80
<b>Adj mean change*</b>	<b>-0.80</b>	<b>-0.48</b>	<b>-0.96</b>
Mean Final Dose	623mg/3.1mg	1500 mg	6.5 mg

\* There were no statistically significant differences between Glucovance and the monotherapies.

Glucovance was not superior to metformin or glibenclamide monotherapy with respect to reduction in HbA1c. Similarly, Glucovance was not superior to metformin or glibenclamide monotherapy with respect to reduction in Fasting Plasma Glucose (FPG) and body weight. At week 26, 68.4% of subjects in the Glucovance group, 59.3% in the metformin group and 67.3% in the glibenclamide group achieved glycaemic control as indicated by an HbA1c < 7%.

- **Efficacy results from the open-label extension phase:**

Results from the open-label extension study are shown in ~~Table 1~~ ~~Table 1~~ ~~Table 1~~. A similar level of glycaemic control was observed for all previous treatment groups after 26 weeks of extended open-label treatment. The subjects enrolled directly in the open-label treatment had a mean change in HbA1c of – 2.46% from baseline to week 26.

**Table 1: HbA1c (%) level changes from baseline (Study 138-059 OL)**

Double-blind treatment group	Week	N	Baseline mean (SE)	On-therapy means (SE)	Change from baseline mean (95% C.I.)
Glucovance	Baseline	51	7.83 (0.25)		
	DB week 26/last prior visit	51	7.83 (0.25)	6.88 (0.24)	-0.95 (-1.43, -0.47)
	OL week 26	46	7.77 (0.26)	7.12 (0.21)	-0.66 (-1.12, -0.19)
Metformin	Baseline	49	8.06 (0.23)		
	DB week 26/last prior visit	49	8.06 (0.23)	7.45 (0.29)	-0.61 (-0.99, -0.23)
	OL week 26	44	8.09 (0.25)	7.37 (0.31)	-0.72 (-1.18, -0.27)
Glibenclamide	Baseline	47	7.74 (0.25)		
	DB week 26/last prior visit	47	7.74 (0.25)	6.81 (0.21)	-0.93 (-1.38, -0.48)
	OL week 26	42	7.65 (0.27)	6.53 (0.22)	-1.11 (-1.65, -0.58)

- **Conclusion on the efficacy of Glucovance in children and adolescents:**

The study failed to demonstrate what it was designed for, i.e. to show the superiority of Glucovance to any of the monotherapies metformin and glibenclamide.

Moreover, the study was conducted with a Glucovance dosage (250/1.25 mg) which is not approved within the EU.

Lastly, 52% of the patients had never previously received any antidiabetic medication. Therefore, the design of this study is not in accordance with the therapeutic indication of Glucovance in adults: the European Summary of Product Characteristics (SPC) of Glucovance mentions that the combination is to be used as “replacement for previous combination therapy with metformin and glibenclamide in patients whose glycaemia is stable and well-controlled”.

- **Summary of safety data in paediatrics:**

#### **Adverse events**

Throughout the study nine non-serious treatment-emergent adverse events (AEs) were reported from 20 adolescent patients. No AEs were reported for the eight children. The most frequently AEs were hyperglycaemia and hypoglycaemia (three events each). There were no serious AEs and none of the subjects discontinued prematurely from the study due to an adverse event. No adverse drug experiences (ADE) are reported since assessment of AEs was done without any regard with the treatment.

During the study and its open label extension no unexpected safety issues emerged. As expected, due to dose-sparing of metformin, patients on Glucovance appeared to have somewhat fewer gastrointestinal complaints than patients on metformin monotherapy and hypoglycaemia appeared related to glibenclamide. Most cases of hypoglycaemia were moderate and could be managed by the subject itself or even without any treatment. No episode of hypoglycaemia required medical assistance.

#### **Conclusion on safety**

Glucovance was generally safe and well tolerated. The overall frequency of adverse events was comparable in the three treatment groups.

## **5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The applicant has complied with the European request to submit data regarding the use of Glucovance in the paediatric population.

The submitted data are based on one pharmacokinetic study and one efficacy and safety study conducted with a Glucovance dosage of 250/1.25 mg, which is not approved in the EU.

Glibenclamide and metformin (the two components of Glucovance) pharmacokinetics were comparable between children and adolescents patients. Based on historical data, C<sub>max</sub> and AUC values for metformin and glibenclamide are comparable between paediatric and adult patients. However, C<sub>max</sub> of glibenclamide was reached much faster in the paediatric patients (compared to adult patients) and the clinical relevance of such differences has not been established.

Although Glucovance was generally safe and well tolerated, its efficacy in children has not been demonstrated, as Glucovance was not superior to metformin or glibenclamide monotherapies. Therefore, no therapeutic indication in children should be granted to Glucovance.

However, a mention of negative results of the clinical study should be added in section 5.1. “Pharmacodynamic Properties” of the SPC. A brief sentence on the main pharmacokinetic results is also deemed appropriate for section 5.2 “Pharmacokinetic Properties”.

#### SPC modifications endorsed:

##### Section 5.1 Pharmacodynamic properties

*In a 26- week, double-blind, active-controlled clinical study performed in the paediatric population, a fixed combination of metformin 250 mg and glibenclamide 1.25 mg was not shown more effective in reducing HbA1c than each of the monotherapies. Therefore, Glucovance should not be used in children.*

Section 5.2 Pharmacokinetic properties

*There were no differences in pharmacokinetics of glyburide and metformin between paediatric patients and weight- and gender-matched healthy adults.*