

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in  
accordance  
with Article 46 of Regulation (EC)  
No1901/2006, as amended**

**Glimepiride**

**NL/W/0022/pdWS/001**

**Marketing Authorisation Holder:  
Sanofi-aventis**

|  |                 |
|--|-----------------|
| <b>Rapporteur:</b>   | The Netherlands |
| <b>Start of the procedure (day 0):</b>   | 29 April 2010   |
| <b>Date of this report:</b>  | 7 April 2011    |
| <b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR)(day 70):</b> | 5 July 2010     |
| <b>Deadline for CMS's comments:</b>  | 23 July 2010    |
| <b>Finalisation procedure (day 90):</b>  | 29 July 2010    |

## ADMINISTRATIVE INFORMATION

|  |   |
|--|---|
| Invented name of the medicinal product:          | Amaryl  |
| INN (or common name) of the active substance(s): | Glimepiride   |
| MAH:   | sanofi-aventis  |
| Currently approved Indication(s)                 | Treatment of type-2 diabetes mellitus (T2DM), when diet, physical exercise and weight reduction alone are not adequate, either as monotherapy or in combination with other antidiabetic agents. |
| Pharmaco-therapeutic group (ATC Code):           | A10BB: Sulfonamides, urea derivatives   |
| Pharmaceutical form(s) and strength(s):          | 1 mg, 2 mg, 3 mg, 4 mg and 6 mg tablets   |

## I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

## II. RECOMMENDATION

The information already approved in the EU SmPC with regard to the paediatric population is appropriate and does not warrant an update of the current EU SmPC [*The MAH considers that all information with regard to the Company Core Safety Information reference should be removed since this is considered as confidential information. The Company Core Safety Information is an internal and confidential document*].

## III. INTRODUCTION

**Glimepiride** is approved for use in T2DM whenever blood glucose levels cannot be controlled adequately by diet, physical exercise and weight reduction alone. Glimepiride may be combined with metformin and other oral antidiabetics and may be used together with insulin. It is available in the following dosage forms: 1 mg, 2 mg, 3 mg, 4 mg and 6 mg tablets.

The aim of this report is to review the clinically relevant information on efficacy and safety relative to glimepiride for the use in **children** with Diabetes mellitus.

To date based on available paediatric data the following paediatric information is available in sanofi-aventis EU SmPC:

### *Section 4.2 Posology and method of administration*

#### Special Populations

*Children and adolescents:*

*There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy (see sections 5.1 and 5.2).*

*The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended.*

### *Section 5.1 Pharmacodynamic properties*

#### Special populations

*Children and adolescents:*

*An active controlled clinical trial (glimepiride up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.*

*Both glimepiride and metformin exhibited a significant decrease from baseline in HbA<sub>1c</sub> (glimepiride -0.95 (se 0.41); metformin -1.39 (se 0.40)). However, glimepiride did not achieve*

*the criteria of non-inferiority to metformin in mean change from baseline of HbA<sub>1c</sub>. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin.*

*Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in paediatric patients.*

## **Section 5.2 Pharmacokinetic properties**

### Special populations

#### *Children and adolescents:*

*A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of glimepiride in 30 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC<sub>(0-last)</sub>, C<sub>max</sub> and t<sub>1/2</sub> similar to that previously observed in adults.*

In accordance with Article 45 of the EU Paediatric Regulation 1901/2006, the two following paediatric studies concerning glimepiride, and completed before 26 January 2007, have been submitted previously by the MAH:

- **HOE490/4045:** An open-label, multicenter, single dose study to evaluate the pharmacokinetics of glimepiride (Amaryl®) in paediatric patients with type 2 diabetes mellitus
- **HOE490/4038:** Glimepiride versus Metformin as Monotherapy in Paediatric subject with type 2 Diabetes Mellitus: A single blind comparison study

The reports of the two above mentioned studies have been submitted early 2008, via a type II variation (MRP NL/H/101/001-005/II/047, or National route depending on the countries), in order to include the corresponding paediatric data into sections 4.2, 5.1 and 5.2 of the SmPC.

In accordance with Article 46 of the EU Paediatric Regulation 1901/2006, the following paediatric study, which has been completed after 26 January 2007, is now submitted by sanofi-aventis:

- **POP6739:** Post-marketing study of Amaryl® (Glimepiride) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study]

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for glimepiride and that there is no consequential regulatory action.

## IV. SCIENTIFIC DISCUSSION

### IV.1 BIOPHARMACEUTICS

No study related to biopharmaceutics that might affect the efficacy and/or safety of glimepiride in children have been performed to date by the MAH, nor was found in the literature.

#### IV.1.1 CLINICAL PHARMACOLOGY

##### IV.1.1.1 PHARMACOKINETICS

Two clinical trials investigating the Pharmacokinetics (PK) in paediatric patients have been performed and sponsored by the Marketing Authorisation Holder (MAH):

**HOE490/4045:** An open-label, multicenter, single dose study to evaluate the pharmacokinetics of glimepiride (Amaryl®) in paediatric patients with type 2 diabetes mellitus

**POP6739:** Post-marketing study of glimepiride (Amaryl®) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study]

**Study HOE490/4045: An open-label, multicenter, single dose study to evaluate the pharmacokinetics of glimepiride (Amaryl®) in paediatric patients with type 2 diabetes mellitus (1)**

#### Objective

To evaluate the pharmacokinetics of a single oral dose of 1 mg glimepiride in paediatric T2DM patients.

#### Study design

Open-label, multicenter, single-dose pharmacokinetic study in paediatric T2DM patients 10 to 17 year old and of various races and ethnicities. Of 43 subjects screened, 30 were enrolled at 8 sites in the United States, received study drug and completed the study.

#### Outcomes

Measurement of serum glimepiride concentrations prior to dose administration and at 1, 2, 3, 4, 6, 8, 12 and 24 hours after dose administration. Serum concentration-time data were analyzed by standard non-compartmental methods. The primary PK endpoints were AUC and  $C_{max}$  of glimepiride. Secondary PK endpoints included  $t_{max}$ ,  $t_{1/2}$ , CL/F, and  $V_{ss}/F$ .

#### Results

There were 4 subjects under 12 years of age and 26 subjects between 12 and 17 years of age. Overall, the majority of the subjects were female, non-white, and overweight (median weight=97 kg, range=56-171 kg). The median HbA1c value in the study population was 9.4%. All subjects reported having experienced symptoms of diabetes; 96.7% had attempted to control the disease with diet and exercise; 46.7% had used antidiabetic drugs; 33.3% had used insulin. All 30 subjects demonstrated

pancreatic reserve after a meal stimulation test. All subjects were evaluable for the primary PK endpoints of AUC and  $C_{max}$ . Secondary PK endpoints were estimated for all but 1 subject who had insufficient terminal phase data.

The PK parameters data were as follows:

| <b>AUC(0-last)<br/>(ng•h/mL)</b> | <b>C<sub>max</sub><br/>(ng/mL)</b> | <b>t<sub>max<sub>a</sub></sub><br/>(hours)</b> | <b>t<sub>1/2</sub><br/>(hours)</b> | <b>CL/F<br/>(mL/min)</b> | <b>V<sub>ss</sub>/F<br/>(L)</b> |
|----------------------------------|------------------------------------|--|------------------------------------|--------------------------|---------------------------------|
| 338.8                            | 102.4                              | 1  | 3.11                               | 58.67                    | 13.69                           |
| ±203.1                           | ±47.7                              | (1 – 6)  | ±1.66                              | ±25.71                   | ±6.09                           |

The overall rate and extent of absorption from the gastrointestinal tract in paediatric subjects 10 year of age and older was similar to that observed previously in healthy adult volunteers and adult patients with T2DM. There was a trend for increasing body weight to decrease overall exposure to glimepiride measured by AUC. A qualitatively similar but less pronounced trend was also evident for  $C_{max}$ . This observation was consistent with a similar effect demonstrated in a previous study of morbidly obese adult patients, in which non-normalized glimepiride AUC and  $C_{max}$  tended to be lower in the obese subjects.

Glimepiride was rapidly absorbed and eliminated in the paediatric subjects studied, with an overall disposition similar to that previously observed in adults administered the same dose and formulation of glimepiride. No clinically important differences in glimepiride exposure among different ethnic subgroups, between males and females, and between subjects <12 and ≥12 years of age were apparent

**Study POP6739 : Post-marketing study of Amaryl® (Glimepiride) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study] (2)**

**Objective**

The primary objective was to investigate the pharmacokinetics of glimepiride in paediatric patients (8 to 16 years of age) with type 2 diabetes in comparison with adults patients (17 years or older of age) with type 2 diabetes. The secondary objective was to evaluate the efficacy using change in HbA1C from baseline to last observation, and the safety in paediatric and adults patients with glimepiride titrated to 80 - <130 mg/dL in FPG, 80 - <130 mg/dL in SMBG and/or <6.5% in HbA1C.

**Study design**

Multicenter, non-comparative, 12-28 weeks, non-blind titration study for duration of treatment between 12 to 28 weeks in 142 subjects enrolled at 34 sites in Japan.

**Results**

Of 142 subjects enrolled, 141 subjects were exposed to glimepiride, 35 in paediatric age groups, and 106 adults. Five subjects had to be excluded from the full analysis set/PK. As a result of population pharmacokinetic analysis, the pharmacokinetics of glimepiride were best described by a one-compartment model (mixture option), with inter-subject variability on clearance (CL/F) and volume of distribution (V<sub>ss</sub>/F) and with a proportional residual error (basic model) under First Order Conditional Estimation.

Screening of covariates resulted in ALT and total bilirubin being most influential for CL/F, and body weight, height, gender and serum creatinine for Vss/F. All these covariates were incorporated into the basic model to build a full model. However, by means of the backward method there was no factor to remain in the final model.

CL/F in the population that was obtained by the final model was 1.56 L/h and Vss was 6.84 L. The individual variation of CL/F was 39.6%, and the residual variation was 45.4%.

Individual PK estimates were obtained by Bayesian estimation using parameter estimates from the final model. CL/F in paediatric subjects and adult subjects was  $1.79 \pm 0.77$  L/h and  $1.64 \pm 0.59$  L/h, respectively, Vss/F was  $6.84 \pm 0.09$  L and  $6.83 \pm 0.11$  L, respectively, and t<sub>1/2</sub> was  $3.15 \pm 1.38$  h and  $3.30 \pm 1.60$  h, respectively. The mean CL/F, Vss/F and t<sub>1/2</sub> were similar in paediatric subjects and adult subjects. Even when subjects received high doses of glimepiride, similar AUC and C<sub>max</sub> were observed in paediatric subjects and adult subjects.

4% of slow absorption subjects were contained in this study population. On comparing of two groups between rapid absorption and slow absorption, the PK parameters showed no difference other than C<sub>max</sub> and T<sub>max</sub>. The background of these two groups was similar and there were no differences in efficacy and safety. This suggests that absorption speed hardly affect efficacy and safety although the cause of slow absorption remains unknown.

There were not clear correlations between the individually estimated parameters, such as CL/F and Vss/F, and the subject characteristics. In the US study HOE490/4045, the effect of body weight on CL/F was observed. However, in this study POP6739, CL/F in a paediatric subject with the lowest body weight (24.0 kg) was 1.82 L/h and no particular decrease in CL/F was observed. Also, the particular decrease in CL/F was not observed in the youngest two subjects who were nine years old and showed 1.79 L/h and 1.82 L/h of CL/F. The relationship of the pharmacokinetic parameters with efficacy (HbA1C and FPG) and safety (the onset of major adverse events) was investigated. This investigation indicated that AUC was slightly related to change in FPG from baseline to endpoint and was not related to change in HbA1C from baseline to endpoint as well as the major adverse events (hypoglycemia or gastrointestinal disorder).

This study demonstrated that when glimepiride (0.5 to 6 mg/day) was administered to Japanese paediatric patients with type 2 diabetes (8 to 16 years of age) and Japanese adult patients with type 2 diabetes (17 years or older of age), the pharmacokinetics of glimepiride were similar between the paediatric patients and the adult patients.

#### **IV.1.1.2 PHARMACODYNAMICS**

No pharmacodynamic study specific to the paediatric population is available.

#### **IV.1.1.3 RAPPORTEUR'S CONCLUSION ON PHARMACOKINETICS AND PHARMACODYNAMICS**

These two studies demonstrated that the pharmacokinetic profile of glimepiride in paediatric population appears similar to the pharmacokinetic profile in adults. No pharmacodynamic study specific to the paediatric population is available.

## IV.1.2 OVERVIEW OF EFFICACY

### IV.1.2.1 INTRODUCTION

This section presents the main features of the glimepiride clinical studies published in the literature and/or performed and sponsored by the MAH, carried out to evaluate its efficacy in a paediatric population.

The literature search was performed on the key terms “glimepiride” and “clinical trials” in “diabetes” through external medical literature databases such as Medline and Embase up to November 2009.

Two studies investigating the efficacy of glimepiride in paediatric population have been performed and sponsored by the Marketing Authorisation Holder (MAH):

**HOE490/4038:** Glimepiride versus Metformin as Monotherapy in Paediatric subject with type 2 Diabetes Mellitus: A single blind comparison study

**POP6739:** Post-marketing study of Amaryl® (Glimepiride) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study]

### IV.1.2.2 Glimepiride and type 1 diabetes in children

#### Wudy et al. 2003 (3)

This study investigated the possible use of glimepiride to increase serum Insulin-Growth Factor I (IGF-I), thus improving glycemic control. 40 pubertal patients with T1DM of a duration superior to 1 year (negative for C-peptide) were randomly allocated at the start of treatment and each participant underwent a 6-week course of either glimepiride (one daily dose of 8.2 µmol = 4 mg; n = 20) or placebo (n = 20) in addition to a multiple injection intensive insulin therapy. One patient receiving glimepiride was withdrawn because of viral encephalitis. The primary end point in the study had been defined as the increment of serum IGF-I between start of treatment and 6 to 8 weeks thereafter. No remarkable changes in IGF-I or IGFBP-3 were observed during glimepiride treatment. When compared with the placebo group, no differences were found. Glimepiride did not influence weight, blood pressure, insulin dosage, fasting serum glucose, rate of hypoglycemias, HbA1c, or serum lipids.

### IV.1.2.3 Glimepiride and type 2 diabetes in children

#### Study HOE490/4038: Glimepiride versus Metformin as Monotherapy in Paediatric subject with type 2 Diabetes Mellitus: A single blind comparison study (4)

#### Background/Methods

This multinational study was active-controlled, randomised and single-blinded. It compared glimepiride to metformin as monotherapy for 24 weeks. A total of 536 paediatric subjects with diabetes type 2 were enrolled and screened, and 285 subjects were randomized. One subject randomized to metformin withdrew before treatment, resulting in 284 subjects in the safety population. A total of 263 (132 glimepiride and 131 metformin) constituted the ITT, 218 (107 glimepiride and 111 metformin) constituted the completer, and 162 (81 glimepiride and 81 metformin) constituted the per-protocol population (aged 8 to 17 years, mean age: 14 years). Glimepiride and metformin doses were titrated based on fasting glucose, with a target of 126 mg/dL (7 mmol/L); titration was limited by hypoglycaemia (for glimepiride) or gastrointestinal side effects (metformin).

## Objectives

The primary objective was to compare the change in glycemic control from baseline to endpoint (last available post treatment assessment) as measured by hemoglobin A1c (HbA1c) in paediatric subjects with type 2 diabetes receiving either glimepiride or metformin as monotherapy.

The secondary objectives were:

To assess any differences in fasting self-monitored blood glucose (SMBG), fasting plasma lipids, and percent completers between paediatric subjects who received glimepiride versus metformin as monotherapy.

To compare the safety of glimepiride versus metformin as monotherapy by assessing episodes of hypoglycemia, body weight, vital signs, adverse events, menstrual patterns, and laboratory values.

## Results

For the safety population, the mean daily dose taken at last visit was 3.6 mg in the glimepiride group, 42% used 1 mg daily as their maximum dose and 31% used 8 mg daily as their maximum dose. The mean dose of metformin was 1373 mg, 60% used 1000 mg daily as their maximum dose and 39% used 2000 mg daily as their maximum dose.

The per-protocol population was used for the primary analyses. The results of the ITT analyses followed the same general pattern as the results of the per-protocol analyses.

The Primary variable: Both glimepiride and metformin exhibited a significant decrease from baseline in HbA1c (glimepiride -0.95 (se 0.41); metformin -1.39 (se 0.40)). The difference between treatments was 0.44% in favour of metformin, but this difference was not statistically significant. Also, no significant difference was observed between treatment groups in the proportion of subjects who achieved HbA1c  $\leq 7.0\%$ , or the time to achieve this endpoint. Because the upper limit of the 95% CI exceeded the predefined limit of 0.3%, the non-inferiority criterion was not met.

The Secondary variables: Decreases in fasting SMBG from baseline were statistically significant at all visits, except at Weeks 4 and 24 for glimepiride; there was no significant difference between the 2 groups. There was no significant difference between the 2 groups in the proportion of subjects achieving SMBG  $\leq 7.0$  mmol/L, or in their time to reach this endpoint. Total cholesterol increased by a mean of 0.206 mmol/L at Week 24 with glimepiride; although clinically a small increment, this increase was statistically significant ( $P = 0.0123$ ). Total cholesterol did not change significantly with metformin.

A non-significant increase from baseline in mean LDL was observed with glimepiride and a non-significant decrease was observed with metformin. The difference between the 2 treatments in changes in LDL from baseline was statistically significant ( $P = 0.0415$ ). There was no significant difference between treatment groups in their change in total and HDL cholesterol and triglycerides from baseline.

There was no significant difference between treatments in their change in BMI from baseline at week 24 for the per-protocol subjects.

Of the safety population, 73% (104/142) glimepiride and 75% (107/142) metformin-subjects completed the study. A similar proportion met the criteria for the completer population: 75% (107/142) glimepiride and 78% (111/142) metformin subjects were completers.

There was no significant difference between treatments for changes in BMI from baseline to Week 24 for the per-protocol subjects.

A mean weight increase of 1.3 kg with glimepiride was statistically significant. Vital signs and menstrual patterns were unchanged.

**Study POP6739: Post-marketing study of Amaryl® (Glimepiride) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study] (2)**

**Objectives**

The primary objective of this multicenter, non-comparative, 12-28 weeks, non-blind titration study was to investigate the pharmacokinetics of glimepiride in paediatric patients (8 to 16 years of age) with type 2 diabetes in comparison with adults patients (17 years or older of age) with type 2 diabetes under steady state. 142 subjects were enrolled at 34 sites in Japan for duration of treatment between 12 to 28 weeks. Duration of study medication in each patient was varied depending on the status of titration.

The secondary objective was to evaluate the efficacy using change in HbA1C from baseline to last observation, and the safety in paediatric and adults patients with glimepiride titrated to 80 - <130 mg/dL in FPG, 80 - <130 mg/dL in SMBG and/or <6.5% in HbA1C.

**Results**

In the Intent-To-Treat (ITT) population, change in HbA1C from baseline to endpoint was  $-0.63 \pm 3.15\%$  in paediatric non-treated subjects,  $-0.32 \pm 1.17\%$  in paediatric treated subjects,  $-0.41 \pm 1.90\%$  in paediatric all subjects and  $-1.50 \pm 1.08\%$  in adult subjects ( $p < 0.0001$ ). HbA1C decreased in each subject group, but there were no significant differences in the paediatric groups.

In the Per Protocol population, however, it was  $-1.86 \pm 2.12\%$  in paediatric non-treated subjects,  $-0.23 \pm 1.12\%$  in paediatric treated subjects,  $-0.61 \pm 1.54\%$  in paediatric all subjects and  $-1.49 \pm 1.06\%$  in adult subjects. Statistically significant differences were observed in paediatric all subjects and adult subjects ( $p = 0.0393$  and  $p < 0.0001$ ).

The proportions of subjects with targeted HbA1C value of <6.5% were 10.0% (1/10) at baseline and 30.0% (3/10) at endpoint in paediatric non-treated subjects, 16.0% (4/25) at baseline and 20.0% (5/25) at endpoint in paediatric treated subjects, 14.3% (5/35) at baseline and 22.9% (8/35) in paediatric all subjects and 0% at baseline and 17.0% (18/106) at endpoint in adult subjects.

In the ITT population, change in FPG from baseline to endpoint was  $19.9 \pm 84.9$  mg/dL in paediatric non-treated subjects,  $-13.1 \pm 46.7$  mg/dL in paediatric treated subjects,  $-3.7 \pm 60.6$  mg/dL in paediatric all subjects and  $-32.0 \pm 34.4$  mg/dL in adult subjects ( $p < 0.0001$ ). Change in FPG from baseline to endpoint in adult subjects was statistically significant ( $-32.3 \pm 35.0$  mg/dL,  $p < 0.0001$ ).

In the ITT population, change in fasting blood glucose by SMBG from baseline to endpoint was  $8.6 \pm 78.7$  mg/dL in paediatric non-treated subjects,  $-31.9 \pm 64.4$  mg/dL in paediatric treated subjects,  $-18.4 \pm 70.5$  mg/dL in paediatric all subjects and  $-32.8 \pm 44.8$  mg/dL in adult subjects ( $p < 0.0001$ ).

The authors conclude that, when glimepiride (0.5 to 6 mg/day) was administered to Japanese paediatric patients with type 2 diabetes (8 to 16 years of age) and Japanese adult patients with type 2 diabetes (17 years or older of age), the pharmacokinetics of glimepiride were similar between the paediatric patients and the adult patients. Glimepiride was also confirmed to be effective and safe in paediatric population as well as in adult population.

#### IV.1.2.4 RAPPORTEUR'S EFFICACY DISCUSSION AND CONCLUSIONS

Few clinical studies are available in the paediatric population. The efficacy of glimepiride is not clear in the treatment of T2DM in paediatric population. In study POP6739, the influence of glimepiride on HbA1c was not statistically significant in the paediatric population. In addition, in this study, the efficacy was less in paediatric patients in comparison to adult patients ( $-0.41 \pm 1.90\%$  in paediatric all subjects and  $-1.50 \pm 1.08\%$  in adult subjects). In study HOE490/4038, the efficacy of glimepiride did not achieve the criteria of non-inferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The results of this study have already been incorporated in the SmPC.

#### IV.1.3 OVERVIEW OF SAFETY

##### IV.1.3.1 INTRODUCTION

This section summarizes the safety data of the glimepiride clinical studies performed by the MAH and carried out in the paediatric population.

Three studies investigating the efficacy and safety of glimepiride in paediatric population have been performed:

**HOE490/4045:** Single dose study evaluating the pharmacokinetics of glimepiride (Amaryl) in paediatric patients with type 2 diabetes mellitus

**HOE490/4038:** Glimepiride versus Metformin as Monotherapy in Paediatric subject with type 2 Diabetes Mellitus: A single blind comparison study

**POP6739:** Post-marketing study of Amaryl® (Glimepiride) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study]

##### IV.1.3.2 ADVERSE EVENTS IN CLINICAL TRIALS

**Study HOE490/4045: An open-label, multicenter, single dose study to evaluate the pharmacokinetics of glimepiride (Amaryl®) in paediatric patients with type 2 diabetes mellitus (1)**

This open-label, multicenter, single-dose pharmacokinetic study which evaluates the pharmacokinetics of a single oral dose of 1 mg in 30 paediatric T2DM patients, is described above.

There were 3 subjects who had pre-dose adverse events and 6 subjects who had treatment-emergent adverse events. Concerning pre-dose adverse events, one subject reported myalgia, one subject had a mild urinary tract infection and the third subject had an abscess of the right posterior thigh that had been treated with incision and drainage and antibiotics between the screening visit and study day. None of these events was assessed as affecting either the subject's participation in the study or the results.

Concerning treatment-emergent adverse events, one subject reported 3 events of dysmenorrhea, 3 subjects reported headache, 1 subject had stomach discomfort, and 1 subject reported upper abdominal pain. The latter event was assessed by the investigator as being possibly related to study drug. All other events were assessed as being unrelated to drug. All of the events were assessed as mild and the subjects recovered without sequelae. There were no serious adverse events and no episodes of hypoglycemia or overdose. No clinically significant changes in fasting plasma glucose were observed.

The authors conclude that a single 1 mg dose of glimepiride administered orally with the last bite of the morning meal was safe and well tolerated by all subjects with no hypoglycemic or serious adverse events.

**Study POP6739: : Post-marketing study of Amaryl® (Glimepiride) in patients with type 2 diabetes to investigate paediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study] (2)**

This multicenter, non-comparative, 12-28 weeks, non-blind titration study is described above.

The incidence of all TEAEs was 71.4% (25/35) in paediatric all subjects [80.0% (8/10) in paediatric non-treated subjects and 68.0% (17/25) in paediatric treated subjects], 65.1% (69/106) in adult subjects and 66.7% (94/141) in total. TEAEs (preferred term) observed in at least 10% of paediatric all or adult subjects were “Nasopharyngitis” {8.6% (3/35) in paediatric all subjects [12.0% (3/25) in paediatric treated subjects] and 12.3% (13/106) in adult subjects}, “Upper respiratory tract inflammation” {17.1% (6/35) in paediatric all subjects [10.0% (1/10) in paediatric non-treated subjects and 20.0% (5/25) in paediatric treated subjects] and 4.7% (5/106) in adult subjects} and “Hypoglycaemia” {8.6% (3/35) in paediatric all subjects [10.0% (1/10) in paediatric non-treated subjects and 8.0% (2/25) in paediatric treated subjects] and 18.9% (20/106) in adult subjects}.

The incidence of ADRs was 11.4% (4/35) in paediatric all subjects [20.0% (2/10) in paediatric non-treated subjects and 8.0% (2/25) in paediatric treated subjects], 24.5% (26/106) in adult subjects and 21.3% (30/141) in total. The ADR (preferred term) observed in at least 5% of paediatric all or adult subjects was “Hypoglycaemia” {8.6% (3/35) in paediatric all subjects [10.0% (1/10) in paediatric non-treated subjects and 8.0% (2/25) in paediatric treated subjects] and 18.9% (20/106) in adult subjects}. The monthly rate of hypoglycemia was 0.0201 episodes in paediatric all subjects (0.0166 episodes in paediatric non-treated subjects and 0.0215 episodes in paediatric treated subjects) and 0.1823 episodes in adult subjects.

The incidence of nocturnal hypoglycemia was 0% in paediatric all subjects and 1.9% (2/106) in adult subjects. The monthly rate of nocturnal hypoglycemia was 0.0070 episodes in adult subjects.

No deaths occurred during the study.

As a serious adverse event, “Mental disorder” was observed in one paediatric treated subject. This event was recovered without sequelae and was considered to be unrelated to the investigational product.

As a TEAE leading to withdrawal from study treatment, “Constipation” was observed in one adult subject. It was not serious and recovered without sequelae. It was considered to be probably related to the investigational product.

The body weight in paediatric all, paediatric treated and adult subjects at endpoint increased ( $p=0.0017$ ,  $p=0.0064$  and  $p<0.0001$ ). The BMI in paediatric all and adult subjects at endpoint increased ( $p=0.0264$  and  $p<0.0001$ ).

The authors conclude that glimepiride was confirmed to be safe in paediatric population as well as in adult population.

## **Study HOE490/4038: Glimepiride versus Metformin as Monotherapy in Paediatric subject with type 2 Diabetes Mellitus: A single blind comparison study (4)**

This multinational active-controlled, randomized, single-blinded study which compares glimepiride to metformin as monotherapy for 24 weeks in 162 paediatric patients suffering from T2DM is described above.

Adverse events were reported with similar frequencies for the glimepiride and metformin treatment groups. The most commonly reported (>5%) treatment-emergent adverse events TEAEs in the glimepiride treatment arm were headache (15/142 [10.6%]), upper respiratory tract infection (10/142 [7.0%]), nasopharyngitis (9/142 [6.3%]) and hyperglycemia (8/142 [5.6%]). In the metformin treatment arm, the most commonly reported TEAEs included headache (17/142 [12.0%]), upper respiratory tract infection (9/142 [6.3%]), diarrhea (11/142 [7.7%]) and nasopharyngitis (10/142 [7.0%]). Most TEAEs were of mild and moderate intensity.

Serious adverse events were reported for 15 subjects; the event occurred before glimepiride treatment was initiated in 1 of these subjects and during the screening phase before randomization for 2 screen failure subjects. Treatment-emergent serious adverse events occurred for 7/142 (4.9%) glimepiride subjects and for 5/142 (3.5%) metformin subjects. The incidence of serious adverse events was similarly low (<5%) in both treatment groups. The incidence of discontinuations from study medication was also similarly low for the 2 groups.

Hypoglycemic episodes occurred in 16% of glimepiride and 13% of metformin subjects. One subject in each group had a severe episode.

No clinically important changes were observed in vital signs and menstrual patterns. Subjects grew a mean of 1 cm in both groups during the study, and a mean weight increase of 1.3 kg was statistically significant in the glimepiride group.

The authors conclude that both glimepiride and metformin were well-tolerated. There were no deaths, pregnancies, study medication overdoses, or clinically important laboratory changes. Adverse events were reported with similar frequencies for the glimepiride and metformin treatment groups. The most frequent possibly treatment-related events were events listed in current labeling for each product.

### **IV.1.3.3 MARKETING EXPERIENCE**

The safety profile of glimepiride is routinely monitored in the post-marketing environment (including patient population of 17 years and younger) and the safety information is presented in the Periodic Safety Update Reports. The glimepiride EU SmPC [*The MAH considers that all information with regard to the Company Core Safety Information reference should be removed since this is considered as confidential information. The Company Core Safety Information is an internal and confidential document*] is updated based on safety analysis to reflect the risk associated with the product. After review of cases reported with use of glimepiride in patients of 17 years of age and younger (~40 reports), it was established that the most commonly reported adverse events were hypoglycemia, gastrointestinal discomfort and hypersensitivity reactions (edema and rash). All of those events are listed in the current glimepiride EU SmPC [*The MAH considers that all information with regard to the Company Core Safety Information reference should be removed since this is considered as confidential information. The Company Core Safety Information is an internal and confidential document*].

The nature of reported events associated with use of glimepiride in paediatric population is compatible with events reported in adult population and did not indicate a new pattern or safety concern not already described in in the current glimepiride EU SmPC. [*The MAH considers that all information with regard to*

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#### **IV.1.3.4 RAPPORTEUR'S SAFETY DISCUSSION AND CONCLUSIONS**

The data provided by three MAH-sponsored clinical trials involving approximately 300 children with T2DM show that short term glimepiride is relatively safe and well tolerated by the paediatric population. However, long term effects are unknown.

### **V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

Limited data are available regarding the use of glimepiride for the treatment of diabetes mellitus in the paediatric population.

The pharmacokinetic profile of glimepiride in paediatric population appears similar to pharmacokinetic profile in adults. No pharmacodynamic study specific to the paediatric population is available.

The efficacy of glimepiride is not clear in the treatment of T2DM in paediatric population. In study POP6739 the influence of glimepiride on HbA1c was not statistically significant in the paediatric population. In addition, in this study, the efficacy was less in paediatric patients in comparison to adult patients. In study HOE490/4038, the efficacy of glimepiride did not achieve the criteria of non-inferiority to metformin.

Short term glimepiride may be relatively safe and well tolerated by the paediatric population. However, long term effects are unknown.

These issues have already been adequately discussed in the EU SmPC. It is concluded that "The available data on safety and efficacy are insufficient in the paediatric population and therefore such use is not recommended".

#### **➤ Overall conclusion**

In conclusion, there is no new relevant clinical data which alters or may result in a new risk/benefit evaluation. Consequently, the information already approved in the EU SmPC with regard to the paediatric population is appropriate and does not warrant an update of the current EU SmPC. *[The MAH considers that all information with regard to the Company Core Safety Information reference should be removed since this is considered as confidential information. The Company Core Safety Information is an internal and confidential document]*

## **VI. REFERENCES**

1. Kovacs S, Harris A. Study HOE490/4045. An open-label, multicenter, single-dose study to evaluate the pharmacokinetics of glimepiride (Amaryl®) in pediatric patients with type 2 diabetes mellitus. February 2005;1016 p.
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