

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Glucobay  
(acarbose)**

**NO/W/0005/pdWS/001**

<b>Rapporteur:</b>	Norway
<b>Finalisation procedure (day 120):</b>	05.08.2011
<b>Date of finalisation of PAR</b>	07.11.2011

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	acarbose
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	A10BF01
Pharmaceutical form(s) and strength(s):	Tablets 50 mg and 100 mg

## I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed by the Rapporteur in section 4.2 and chapter 3, respectively. Please see section IX of this report

## II. RECOMMENDATION<sup>1</sup>

The Rapporteur considers the data on acarbose insufficient to give any advice on paediatric use. If the current SmPC/PL is lacking paediatric information, a change to the SmPC in section 4.2 and to the PL in chapter 3, is proposed.

A Type IB variation on the proposed changes to the SmPC/PL should be submitted by the MAH by 04.10.2011, if not already included.

## III. INTRODUCTION

Bayer Schering Pharma AG submitted 7 completed paediatric studies (6 in type 1 diabetes mellitus (T1DM) subjects and 1 in impaired glucose tolerance (IGT) subjects), a Bayer data pool report comprising all paediatric patients aged  $\leq 16$  years who were treated with acarbose for diabetes or obesity as well as a review of 6 published studies and 3 case reports for acarbose, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical clinical overview has also been provided.

According to additional information from the marketing authorisation holder (MAH), acarbose is currently marketed in the European Union for the indication type 2 diabetes mellitus (T2DM) (10 countries), T2DM + IGT (1 country), T1DM + T2DM (11 countries) and T2DM + T1DM + IGT (1 country). Currently, acarbose is not recommended in the European Union for use in children or adolescents below the age of eighteen due to insufficient data on safety and efficacy.

In contrast to the original submission, in response to the Draft Day 89 Paediatric Assessment Report the MAH proposed changes to sections 4.2, 4.4, 4.8 and 5.1 of SmPC, please see section VIII of this report.

## IV. SCIENTIFIC DISCUSSION

### Diabetes in children

Diabetes is one of the most common chronic diseases in childhood and can strike children at any age, including pre-school children and toddlers. Diabetes in childhood increases the risk of life-threatening diabetes complications at an early age with a potential shortening of life expectancy.

Type 1 diabetes is the predominant form in children. The incidence of childhood onset type 1 diabetes is increasing in many countries in the world, at least in the under 15-year age group. There are strong indications of geographic differences in trends but the overall annual increase is estimated to be around 3%. There is evidence that incidence is increasing more steeply in some of the low [prevalence](#) countries such as those in central and eastern Europe. Moreover, several European studies have suggested that, in relative terms, increases are greatest in young children.

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<sup>1</sup> The recommendation from section V can be copied in this section.

Type 2 diabetes has been recently emerging among – mostly obese - children in puberty in all countries, whether poor or rich (ref IDF; Diabetes in the Young, 2010, <http://www.diabetesatlas.org/book/export/html/38>). An important feature of type 2 diabetes in adolescence is the higher insulin resistance and faster beta cell destruction rate relative to adults.

#### Product characteristics

Acarbose is an inhibitor of alpha glucosidases, especially sucrase. This slows the digestion and absorption of carbohydrates in the small intestine and hence reduces the increase in blood-glucose concentrations after a carbohydrate load.

### **IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)**

From the brief documentation provided by the MAH, the pharmaceutical formulations used in most studies were 50 mg tablets. The tablets were administered with meals.

### **IV.2 Non-clinical aspects**

No non-clinical documentation was provided.

### **IV.3 Clinical aspects**

#### **1. Introduction**

This section presents the main features of the acarbose clinical studies published in the literature and/or performed and sponsored by the MAH, carried out to evaluate its efficacy and safety in a paediatric population. The assessment in this report will focus on studies comprising children and/or adolescents < 18 years with diabetes mellitus.

Table 1 gives an overview of the studies performed by MAH, the patients included, the doses administered and the respective treatment durations.

**Table 1: Overview of Clinical Studies Performed by Bayer**

Report no.	Date of report	Study no.	Indication	No. of children receiving at least one dose of acarbose	Age [years]	Acarbose dose [mg/d]	Duration [days]
<b>Insulin-dependent diabetes mellitus</b>							
PH-9873	03-NOV-1980	BAY-G5421-0160	IDDM	4	15 – 17	400 – 450	14 – 21
PH-10448	12-NOV-1981	BAY-G5421-0221	IDDM	10	8 – 16	150	42 – 84
PH-10484	26-NOV-1981	BAY-G5421-0234	IDDM	11	11 – 16	150 – 300	84
PH-14352	10-DEC-1985	BAY-G5421-0428	IDDM	12	10 – 15	150	10
PH-23433	21-OCT-1994	BAY-G5421-0634	IDDM	15	8 – 16	200	118
PH-24820	16-FEB-1996	BAY-G5421-0665	IDDM	12	9 – 16	200	84
PH-19234	10-JUL-1990		Data pool (total)*	73	≤ 16	50 – 600	1 – 104
			IDDM*	65	5 – 16		
			Obesity	8	≤ 16		
Data pool analysis of paediatric patients (aged ≤ 16 years) included in acarbose studies. The data pool is comprised of paediatric data originating from a total of 23 studies.*							
<b>Impaired glucose tolerance</b>							

Report no.	Date of report	Study no.	Indication	No. of children receiving at least one dose of acarbose	Age [years]	Acarbose dose [mg/d]	Duration [days]
PH-26068	06-MAR-1997	BAY-G5421-0696	Cystic fibrosis with IGT	8	8 – 17	150	5
Total number of paediatric patients in Bayer studies				110 (IDDM: n=102)			

IDDM: Insulin-dependent diabetes mellitus; IGT: Impaired glucose tolerance

\* Included are all patients aged  $\leq$  16 years (n=34) from reports PH-9873, PH-10448, PH-10484 and PH-14352 above.

The literature search was performed through external medical literature databases such as Medline and Embase, Biosis, Current Contents, Derwent Drug File and the company's Product Literature Database to identify any articles mentioning the use of acarbose in children or adolescents, regardless of the indication in August 2009. In the interim period since then, no further relevant publications have been identified.

Table 2 gives an overview of the identified publications.

**Table 2: Overview of Published Studies and Case Reports on the Use of Acarbose in Children**

Reference Study design	Population	No. of pts	Age [years]	Dose [mg/d]	Duration [days]*
<b>Insulin-dependent diabetes mellitus</b>					
[5] Bartsocas C (1982) Sequential	IDDM	9	7-15	150-200	56
[6] Krahl A (1984) Uncontrolled	IDDM	8	11 $\pm$ 2	100-275	84
<b>Impaired glucose tolerance</b>					
[7] Burgert TS (2008) Uncontrolled	Obesity with IGT	8	15 $\pm$ 1	150	42
<b>Other indications</b>					
[16] Ng D (2001) Uncontrolled	Postprandial hypoglycaemia secondary to Nissen fundoplication	6	0.3-2	12.5-50 mg per feeding	NR
[17] Gröbe H (1983) Sequential	Glycogen storage disease I	4	NR	15 mg/kg	7-9 days
[18] Hoekstra J (1996) Uncontrolled	Healthy subjects	5	11-18	200	2 single doses
[19] Rating D (1982) Placebo-controlled	Healthy subjects (n=7), IDDM (n=4)	11	4-14	50	Single dose
<b>Case reports</b>					
[20] Dura Trave T (1999)	Reactive postprandial hypoglycaemia	1	9	150	~365
[21] Zung A (2003)	Postprandial hypoglycaemia secondary to Nissen fundoplication	1	1	50	~420
[22] Yigit S (2002)	Type 2 diabetes	1	16	NR	NR
Total number of paediatric patients in the literature		54 (IDDM: n=21)			

IDDM: insulin-dependent diabetes mellitus; IGT: impaired glucose tolerance; NR: not reported

\* Duration of active (acarbose) treatment phase.

No clinical pharmacology studies in paediatric patients were performed by Bayer or reported in the literature.

## 2. Clinical studies

## ***Acarbose in children with diabetes mellitus***

**Report PH-9873 (Study No. BAY-G5421-0160)** – *The effect on the daily blood-glucose profile and on the insulin consumption by an "artificial pancreas".*

Altogether 15 patients were included in the study, 4 of whom were aged between 15 and 17 years. Since the data were not analysed for paediatric and adult patients separately, the efficacy summary referred to the entire study population.

Assessor`s comment:

*This study comprised only 4 children out of total 15 patients.*

*Considering that no separate analysis were performed for paediatric patients, the results from this single-blind study are of less importance and are therefore not further described.*

**Report PH-10448 (Study No. BAY-G5421-0221)** - *The effect of acarbose on the insulin consumption of children treated with insulin.*

➤ **Description**

This study was a randomised, double-blind cross-over comparison with placebo.

No exact information about time of study conduct is available, however the study report is dated 12. November 1981.

➤ **Methods**

- Objective(s)

Consumption of insulin during therapy with acarbose.

- Study design

16 outpatient children treated with insulin were included in the study and divided into 2 treatment groups according to a random code: group I initially took acarbose for 6 weeks and then placebo for a further 6 weeks. In group II, the treatment with drug and placebo was in the reverse order.

Insulin consumption, dietary regimen, tablet intake, symptoms and results of self-monitoring of urinary glucose concentrations were recorded in a diary by the patients. Further parameters to be determined prior to the study and at the end of each treatment period were blood glucose concentrations (at 8.00, 12.30 and 16 .00 hours) and the percentage of glycosylated haemoglobin.

- Study population /Sample size

10 insulin-dependent children with type 1 diabetes mellitus were included in the study.

- Treatments

The dosage of acarbose was one tablet containing 50 mg at each of the three main meals for children aged up to 12 years. For older children the dose was doubled.

- Outcomes/endpoints

Please refer to Study design.

➤ **Results**

- Recruitment/ Number analysed

Of the 10 included children, the treatment was discontinued on the 3rd day for one child because of intestinal complaints.

- Baseline data

For the total group of 9 patients remaining in the study, the mean ( $\pm$  SD) age was  $11 \pm 4$  years, the mean body weight  $37 \pm 11$  kg, and the mean height  $147 \pm 18$  cm. Four of the 9 patients were girls. The mean known duration of diabetes was  $4 \pm 2$  years. The mean daily dose of insulin administered was  $29 \pm 17$  units. The dose of acarbose reported throughout for all the patients was  $3 \times 50$  mg per day.

- Efficacy results

Due to deviations from the envisaged randomisation, differing durations of treatment and especially the considerable heterogeneity of both treatment groups, together with isolated values missing, no reasonable statistical analysis of this study was possible.

The examination of the individual courses showed that the consumption of insulin generally increased somewhat during the study. This increase seemed to have been somewhat less under acarbose than under placebo, however no mean values were given. The excretion of glucose in the urine under acarbose was usually lower than under placebo. The percentage of glycosylated haemoglobin increased throughout the study, but to a much lesser degree during treatment with acarbose. A similar, though less pronounced, response was found for blood glucose concentrations.

- Safety results

One patient left the study due to gastrointestinal complaints and 2 other patients had flatulence or abdominal pains on 1-2 days under acarbose. The hypoglycaemia or symptoms leading to a suspicion of hypoglycaemia in one patient was approximately equally distributed during the treatments with placebo and acarbose. Some laboratory values were missing, however the laboratory investigations did not seem to reveal any drug related abnormalities.

Assessor's comment:

*The efficacy results did not reveal any significant difference between the treatment groups. Given the mechanism of action and the study population in question, no unexpected adverse events seem to have occurred. Due to the serious flaws in study conduct described above, this small study is considered to have very limited scientific value.*

**Report PH-10484 (Study No. BAY-G5421-0234) - Effect of 3 months of acarbose therapy on the glycosylated haemoglobin content in the blood of children treated with insulin.**

➤ **Description**

This open, single-blind, uncontrolled study investigated the effect of acarbose therapy compared to placebo.

No exact information about time of study conduct is available, however the study report is dated 16. November 1981.

➤ **Methods**

- Study design

Insulin-dependent out-patients aged between 8 and 14 years were treated for 12 weeks with acarbose after a determination of the preliminary values. This was followed by an equal wash-out period on placebo. At the end of the two treatment periods the fraction of HbA1c in the blood, the post-prandial blood-glucose concentration 1 h after lunch, the glucose content in the urine samples collected in the afternoon, overnight, and before noon, and the body weight were determined, and various laboratory investigations were performed to evaluate the drug's tolerability.

- Study population /Sample size

To reach the planned number of 10 evaluable patients, 13 patients were included in the study.

- Treatments

The initial dose was 1 acarbose tablet of 50 mg at each of 3 mealtimes and, depending on the tolerability, this was increased to a maximum of 3 x 100 mg or reduced to 3 x 50 mg per day.

- Outcomes/endpoints

Change in HbA1c.

- Statistical Methods

All the information and data on the patients were compiled in the form of lists.

The reorganized group (n = 10) was described by mean values, standard deviations, and medians with minimum and maximum values. In the case of qualitative characteristics the absolute frequencies were given.

➤ **Results**

- Recruitment/ Number analysed

Of the 13 included patients, 2 dropped out prematurely, and in 1 case the treatment was discontinued 3 weeks before the appropriate investigations could be carried out. Only 3 of the children were between the envisaged age limits; the others were all older, whereof two were 18.

- Baseline data

Baseline data were recorded for ten patients. Four of the children were boys, the average age was  $15 \pm 2$  years, height  $163 \pm 11$  cm, weight  $56 \pm 11$  kg. The duration of diabetes was  $82 \pm 39$  months and that of insulin therapy  $79 \pm 39$  months. The mean daily dose of the insulin was  $49 \pm 11$  units (U). This daily dose was always given in 2 individual fractions.

- Efficacy results

HbA1c under acarbose therapy was lower than before the start of the study and under placebo (pre-study value  $8.0 \pm 2.0\%$ , acarbose value  $7.5 \pm 1.5\%$ , placebo value  $7.9 \pm 1.8\%$ ). The daily insulin doses showed a tendency to decrease under acarbose (pre-study value 51 units, acarbose value 46.4 units, placebo value 47.4 units). The mean postprandial glucose concentrations were lowest under acarbose (pre-study value  $164 \pm 76$  mg/dl, acarbose value  $143 \pm 63$  mg/dl, placebo value  $201 \pm 98$  mg/dl). Glycosuria was found to markedly improve under acarbose. The mean weight gain was virtually the same for acarbose and placebo.

- Safety results

Five patients reported intestinal symptoms. The following intestinal complaints were reported: flatulence, meteorism, abdominal pains, increased frequency of stools or a tendency towards diarrhea. The two cases of discontinuation of the therapy were, according to the applicant, not drug related. One patient in the third week of the treatment suffered from hypoglycaemia accompanied by loss of consciousness.

The laboratory values showed strong interindividual and intraindividual variations, however the variations seem not to be related to study drug.

Assessor`s comment:

*Overall there was a tendency that HbA1c decreased somewhat more in the acarbose group compared to the placebo group. Given the mechanism of action and the study population in question no unexpected adverse events seem to have occurred. However, there are several limitations to this study (e.g. open, single-blind, uncontrolled, very small sample size (only 3 between the envisaged age limits), and therefore it is of very limited scientific value.*

**Report PH-14352 (Study No. BAY-G5421-0428) - Biometrically designed observation study with acarbose treatment and with preliminary and follow-up placebo periods in diabetic children (Type I).**

## ➤ **Description**

No exact information about time of study conduct is available, however the study report is dated 10. December 1985.

This was a non-randomised observation study.

## ➤ **Methods**

- Objective(s)

This study was designed to investigate whether acarbose improved the metabolic status in diabetic children in comparison to placebo, under inpatient and outpatient conditions.

- Study design

After a preliminary 7-day period, patients were given placebo for 10 days, then 3x50 mg acarbose daily for 10 days, and finally placebo again for a further period of 10 days. The patients were put on an isocaloric diet corresponding on average to 2214 kcal and comprising 54% carbohydrates, 25% fats, and 21% protein.

- Study population /Sample size

10 or more children with T1DM, age: > 10 to < 15, duration of diabetes: > 18 months without remission.

- Treatments

Please refer to Study design.

- Outcomes/endpoints

Fasting blood glucose, postprandial blood glucose, urinary glucose and daily insulin dose.

- Statistical Methods

Only descriptive statistics were presented. Mean values and standard deviations were calculated for the description of the group, as were the medians and minimum and maximum values for the blood glucose, urinary glucose, age, weight, height, and the duration of diabetes. The areas under the curve were also calculated for the daily blood-glucose profile. The mean changes (mean values before and after treatment) were calculated for the tolerability parameters and plotted graphically in correlation diagrams.

## ➤ **Results**

- Recruitment/ Number analysed

12 T1DM children took part in the study.

- Baseline data

The patients (6 boys and 6 girls) had an average age of  $13 \pm 1$  year, an average weight of  $42 \pm 5$  kg, and an average height of  $151 \pm 9$  cm. Duration of diabetes were on average 34 months (= median value, range 17 - 20 months), and was initially treated with  $35 \pm 10$  units of insulin/day.

- Efficacy results

The mean fasting blood glucose values (7:00 a.m.) decreased from  $208 \pm 109$  mg/dl at the end of the first placebo period to  $149 \pm 57$  mg/dl at the end of the acarbose treatment period, and during the second placebo period increased again to  $161 \pm 65$  mg/dl. The postprandial blood glucose after breakfast (9:00 a.m.) decreased from  $293 \pm 83$  mg/dl at the end of the first placebo period to  $221 \pm 96$  mg/dl under acarbose and then remained unchanged in the second placebo period ( $220 \pm 91$  mg/dl). The postprandial values in the early afternoon also decreased from  $205 \pm 76$  mg/dl in the first placebo period to  $178 \pm 85$  mg/dl under acarbose, and rose in the second placebo period to  $231 \pm 112$  mg/dl. The mean urinary glucose excretion (g/24h) at the end of the acarbose period was, at a median of 0 g (range 0–20 g), distinctly lower as compared to the first placebo period (median 9.8 g, range 0–66 g)

and to the second placebo period (median 11.4 g, range 0–30 g). The mean daily insulin dose remained practically unchanged throughout the study, as did the mean body weight.

- Safety results

There was only one report of intestinal side effects (meteorism, diarrhoea). Of the 12 children, all but 3 complained of hunger as a side effect at some stage, under either or both treatments. Laboratory investigations did not indicate any intolerability.

Assessor`s comment:

*The acarbose group seemed to achieve better results than placebo group with respect to fasting blood glucose, postprandial blood glucose and urinary glucose. Given the large standard deviations, no firm conclusions can be drawn. No difference was seen for daily insulin dose and body weight. Given the mechanism of action and the study population in question, no unexpected adverse events seem to have occurred. As this is only a non-randomised observational study including only a few patients, the results are of limited significance.*

**Report PH-23433 (Study No. BAY-G5421-0634)** - *Clinical study to investigate the efficacy and tolerability of acarbose versus placebo in diabetic children receiving conventional insulin treatment, with particular regard to variations in the blood glucose level.*

➤ **Description**

Time of study: May 1991 to March 1992.

This study was a unicentre, randomised, placebo-controlled, double-blind, two-arm group comparison in T1DM.

➤ **Methods**

- Objective(s)

The objective of this study was to investigate the effect of acarbose, versus placebo, on parameters of metabolic control, including the difference between daily maximum and minimum blood glucose concentrations, and acarbose's tolerability in out-patient diabetic children receiving conventional insulin treatment.

- Study design

The study was to consist of a screening-visit, 6 to 1 week prior to randomisation, and 4 visits to the clinic during the 18 weeks of treatment. In addition to measurements at the clinic visits, patients were to perform daily self-monitoring of:

- urine glucose, in the morning (test strips)
- urine acetone, in the morning (test strips)
- insulin dose (regular, intermediate-/long-acting insulin), morning, evening

Self-monitoring for 7 days in each of weeks -1, 6, 12 and 18 were required for:

- symptoms of hypoglycaemia at night
- blood glucose (test strips, measurement with Glucometer III) several times during the day

- Study population /Sample size

31 patients were randomised, 15 to the acarbose- and 16 to the placebo-group.

- Treatments

The patients were to be treated for 18 weeks with either 50 mg acarbose four times a day, (with the first mouthful of the three main meals and the late snack) (= 200 mg/day) or 1 tablet acarbose-placebo four times a day.

- Outcomes/endpoints

Primary efficacy criterion: the difference between the maximum and the minimum blood glucose concentration each day, expressed as a mean of the values obtained over 7 days of self-monitoring. Secondary efficacy criteria: HbA1c fructosamine, urinary glucose, hydroxybutyrate/creatinine ratio, and cortisol/creatinine ratio.

- Statistical Methods

All parameters documented in the case report forms and the patients' diaries were analysed descriptively and the results given in tables and figures, sorted according to treatment group. The influence of the treatment group on the primary efficacy criterion was calculated by analysis of covariance, taking into account the baseline values.

## ➤ Results

- Recruitment/ Number analysed

4 of the 31 randomised patients had to be excluded from the analysis of efficacy, all of them belonging to the placebo-group: Patient no. 1 dropped out of the study after 44 days of treatment; for the patients nos. 8, 9, and 25, the patient's diaries were filled in incompletely and a calculation of the primary efficacy criterion was not possible.

- Baseline data

The acarbose group consisted mainly of girls (5 boys, 10 girls) whereas the placebo group consisted mainly of boys (7 boys, 5 girls). The mean ( $\pm$  SD) age was  $12.40 \pm 2.23$  years in the acarbose, and  $11.92 \pm 3.03$  years in the placebo group. The patients in the acarbose group were (means  $\pm$  SD)  $155.8 \pm 13.2$  cm tall and weighed  $50.5 \pm 14.6$  kg and a mean HbA1c value of  $7.72 \pm 1.40\%$ . The children receiving placebo were  $150.3 \pm 14.5$  cm tall and weighed  $43.8 \pm 13.7$  kg and a mean value of HbA1c of  $7.99 \pm 1.82\%$ . The median duration of diabetes was 63 (8-150) months in the acarbose and 51 (16-156) months in the placebo group.

- Efficacy results

An effect of acarbose as compared to placebo on the difference between the daily blood glucose maximum and minimum (primary efficacy criterion) could not be detected. The measurement was done at home by the patients or by their parents five times per day for one week, both before and every 6 weeks during the study, using test strips and Glucometer III. For HbA1c and fructosamine, no relevant differences between acarbose and placebo treatment could be seen. Furthermore, during the study period in 50% of the days patients under placebo treatment did not excrete glucose with their urine compared to 69% of the days in the acarbose group.

- Safety results

No patients in the acarbose group dropped out of the study. 19% of the placebo group and 60% of the acarbose group showed adverse events, in both groups mainly mild to moderate intestinal symptoms like meteorism or flatulence. Hypoglycemic events were observed in 3 and 1 subjects in the acarbose arm and placebo arm, respectively. These events were considered related to simultaneously insulin therapy and all were resolved. Laboratory investigations gave no hint of any intolerability.

Assessor's comment:

*There was no difference with respect to the primary and secondary endpoint between the two treatment groups in this small study. According to the applicant, a possible explanation for the lack of efficacy might be methodological deficiencies (insufficient number of daily measurements and an insufficient accuracy of home monitoring methods using test strips and Glucometer III).*

*This might be a plausible explanation, however one must also take into account the limited study population. No firm conclusions can be drawn from this study.  
Given the mechanism of action and the study population in question no unexpected adverse events seem to have occurred.*

**Report PH-24820 (Study No. BAY-G5421-0665)** - *Clinical study on the efficacy and tolerability of acarbose compared with placebo in diabetic children on conventional insulin treatment, in particular with observation of the glycemc control index.*

➤ **Description**

Time of study: September 1991 to September 1993.

This was a randomised, double-blind, 2-arm group comparison study in outpatients at a single centre.

➤ **Methods**

• Objective(s)

The objectives of this study were to determine acarbose's efficacy with special regards to fluctuations in the daily blood glucose profile and tolerability compared to placebo in diabetic children.

• Study design

After a screening visit the patients were randomised and received the study medication for a period of 12 weeks. They visited the centre prior to, during and at the end of the period of intake of study medication.

• Study population /Sample size

The calculated sample size required was 11 per group; thus, 15 patients per group, i.e. a total of 30 patients, should have been enrolled into the study to allow for drop-outs.

• Treatments

The patients were to take a daily dose of either 4 x 1 tablet containing 50 mg acarbose (= 200 mg/day) or 4 x 1 placebo-tablet. The tablets were to be taken with the first mouthful of each of the three main meals and the late snack.

• Outcomes/endpoints

Primary efficacy parameter: Glycemic Control Index (GCI) after 12 weeks of treatment as compared to the baseline value.

Secondary efficacy parameters : HbA1c, fructosamine, and urine glucose.

• Statistical Methods

The Glycemic Control Index (GCI) after 12 weeks of treatment, were calculated from the blood glucose (BG) profiles (9 determinations within 24 h):

$$\text{GCI} = \text{mean BG} + (\text{BGmax} - \text{BGmin})/2$$

This endpoint was to be evaluated with an analysis of covariance, taking the GCI-prevalues from day 0 as covariate and the treatment group as factor. All other analyses were to be done descriptively in an exploratory sense. Due to an error contained in the protocol (first intake of study drug with lunch on the day of the blood glucose profile) no GCI-prevalues without study medication were available, and an analysis of covariance as primary analysis could not be carried out.

➤ **Results**

• Recruitment/ Number analysed

The study was prematurely terminated due to difficulties in patient recruitment, however 25 patients were enrolled into this study; 12 into the acarbose group and 13 into the placebo group. All of them were valid for safety analysis. 1 patient of the placebo group dropped out of the study due to adverse events 9 days after having started taking the study medication. Therefore, 24 patients were valid for the analysis of efficacy (acarbose: 12, placebo: 12)

- Baseline data

The acarbose group consisted mainly of girls (5 boys, 7 girls), so did the placebo group (4 boys, 9 girls). The mean ( $\pm$  SD) age was  $13 \pm 2.4$  years in the acarbose group, and  $13 \pm 1.3$  years in the placebo group. The patients in the acarbose group were (means  $\pm$  SD)  $161 \pm 14$  cm tall and weighed  $53 \pm 17$  kg. The children receiving placebo were  $163 \pm 7$  cm tall and weighed  $53 \pm 9$  kg. The median duration of diabetes was 49 (range: 25-100) months in the acarbose and 42 (range: 101-55) months in the placebo group. The GCI at screening were  $14.3 \pm 1.5$  (acarbose) and  $16.4 \pm 2.7$  (placebo). The baseline HbA1c was similar between the two groups ( $10.2\% \pm 1.8$ , vs.  $10.3\% \pm 1.5$ ).

- Efficacy results

No statistically significant differences between acarbose and placebo treatment, given in addition to conventional insulin therapy, could be detected with respect to the GCI ( $13.6 \pm 3.1$  in the acarbose group and  $12.0 \pm 3.1$  in the placebo group). As possible reasons, the lack of valid baseline values and/or the lack of suitability of the GCI to reflect the efficacy of acarbose should be considered.

- Safety results

No patient of the acarbose group dropped out of the study. 33% of the acarbose- and 18% of the placebo-treated patients showed mild or moderate adverse events, mainly (acarbose: exclusively) intestinal symptoms. A reduction in hypoglycemic episodes and nocturnal hypoglycemia were reported. Laboratory investigations gave no hint of any intolerance to the study medication.

*Assessor's comment:*

*No differences between treatment groups were detected. There were several limitations to this study (no valid baseline values, small study, GCI-values differed prior to the study and somewhat higher insulin dose in the placebo group). No firm conclusions can be drawn from this study. Given the mechanism of action and the study population in question, no unexpected adverse events seem to have occurred.*

**Report PH-19234 (Paediatric Data Pool) - Assessment of efficacy and tolerability of acarbose in children under 16 years.**

The efficacy and tolerability of acarbose was investigated in children with diabetes mellitus (n=73) on the basis of a data pool analysis comprising paediatric data originating from a total of 23 studies. Included in this analysis are all patients aged  $\leq 16$  years (n=34) from reports PH-9873, PH-10448, PH-10484 and PH-14352 above.

65 of the 73 children were treated with acarbose for diabetes mellitus, and 8 for obesity. All 65 diabetes patients were type I diabetics and the data pool analysis focuses on this group. The mean ( $\pm$  SD) age of the 65 children with diabetes was  $12.7 \pm 2.6$  years. The majority of the children were female (n=35). The boys weighed  $42.3 \pm 14.3$  kg and were  $150.9 \pm 18.4$  cm tall while the girls weighed  $43.4 \pm 9.7$  kg and were  $151.3 \pm 10.9$  cm tall. The mean ( $\pm$  SD) disease duration was  $62 \pm 46$  months for the boys and  $60 \pm 32$  months for the girls. The majority of the children (n = 34) received a daily dose of  $>150$  to 300 mg acarbose. Most of the cases (n = 46) were treated for up to 74 days with acarbose. During acarbose therapy, a clear reduction in postprandial blood glucose values was observed. With acarbose, the mean lowering of the blood glucose levels 2 hours postprandially was 42 mg/dl as compared to the baseline value. The reduction in the fasting values was far less marked (-11 mg/dl). Excretion of urinary glucose (g/24 h) also decreased by the end of therapy (-14 g/24 h). A

mean reduction in HbA1c of 0.57 percentage points was achieved. Rather more marked was the reduction in HbA1c in patients with treatment duration of  $\geq 2$  months (-0.78 percentage points).

Five children (6.9%) prematurely discontinued treatment with acarbose. Therapy was discontinued in 2 patients on account of gastrointestinal events, in 1 patient on account of other adverse events. The other reasons for discontinuation were either non-medical (n=1) or concomitant diseases (n=1). Of 73 children, 37 (50.7%) reported adverse events, in some cases several per person. The number of patients with digestive side-effects (mainly flatulence and diarrhea) was 30 (41%). At the end of therapy the laboratory target parameters showed no noticeable differences from the baseline values in the entire group of children (n=73).

Assessor`s comment:

*Explanation on how the included studies were selected is lacking. As this does not have any impact on the Rapporteur`s conclusion and recommendation, it is accepted, although not optimal. The lowering of HbA1c achieved with acarbose was as expected and previously reported. Due to the heterogeneous population, and the lack of significance testing, the results of these evaluations are to be regarded as an explorative data analysis. Therefore, they are of limited significance. No unexpected adverse events seem to have occurred.*

### ***Acarbose in children with impaired glucose tolerance***

**Report PH-26068 (Study No. BAY-G5421-0696) - Double-blind, cross-over clinical study at a single centre to compare acarbose with placebo in respect of efficacy and tolerability in patients with cystic fibrosis and pathological glucose tolerance (pilot study).**

The 12 patients enrolled into this study were 8 to 22 years of age (median: 15 years). Eight patients were below the age of 18, however no separate analysis was performed for this group.

Assessor`s comment:

*No separate analyses were performed for paediatric patients. Thus, the results from this study are of less importance and are therefore not further described.*

### ***Published Data on Clinical Efficacy and Safety***

Two studies investigated the use of acarbose in children with diabetes mellitus.

*Bartsocas et al. - Acarbose as an adjunct in the management of juvenile-onset diabetes (1982).*

This study evaluated the efficacy and tolerance of acarbose in nine type 1 diabetes patients aged 7 to 15 years. All participants received placebo for two weeks before entering active treatment of acarbose 150 or 200 mg in two divided doses for 8 weeks, followed by a 2-week placebo phase. HbA1c, 2-hour postprandial blood glucose and quantitative urinary and protein measurements were studied. Three patients were withdrawn from the study prior to its completion though no reasons for study discontinuation were given. HbA1c levels decreased from a mean of 11.3% to 10.3%, postprandial blood glucose decreased from 293 to 227 mg/dl and five patients were able to decrease their insulin requirements. No drug side effects were reported. Overall, no unexpected, clinically relevant laboratory abnormalities seemed to have occurred.

*Krahl A. - The effect of the alpha glucosidase inhibitor (Bay G 5421) on the metabolism of adolescent diabetics (type 1) in a long term study (1984).*

This uncontrolled study included 8 children (6 girls and 2 boys) aged  $11 \pm 2$  years who had been diagnosed with IDDM  $6 \pm 3$  years before the study. The children were treated with acarbose for 12 weeks at a daily dose of 100-275 mg divided into 2 doses. Daily blood glucose profiles, 2-hour postprandial blood glucose concentrations, urinary glucose excretion, and HbA1c were measured. Insulin doses were not changed during this study.

Acarbose therapy was associated with decreased median glucose levels in the daily blood glucose profiles. The mean 2-hour postprandial blood glucose concentration decreased from a pre-treatment level of 16.4 mmol/l to less than 10 mmol/l after 10 days of acarbose treatment and remained around this value on most days throughout the 12-week study period. Median urinary glucose excretion decreased from 33.2 g/d (range: 1.8-67.0 g/d) at baseline to 16.2 g/d (range: 2.1-33.0) on day 28, but increased to 26.9 g/d (range: 0.0-39.5 g/d) by day 84. Body weight increased on average by 2.5 kg per child over the 3-month period of this study. HbA1c levels did not change substantially during acarbose treatment. GI AEs were reported in all subjects. The severity of these events declined over time.

**Assessor`s comment:**

*The results from these preliminary studies are interesting, but due to small sample size and lack of control group of limited scientific value.*

*The Krahl article is available in German only. This is accepted as the study is considered of limited value.*

One study investigated the use of acarbose in children with Impaired Glucose Tolerance.

*Burgert TS et al. - A Pilot Study Using Acarbose to Improve Glycemic Excursions in Pre-Diabetic Obese Youth (2008).*

This uncontrolled study enrolled 8 obese children whose mean age was  $15.2 \pm 1.1$  years. All subjects underwent an oral glucose tolerance test (OGTT) and 72 hours of ambulatory, continuous glucose monitoring at baseline and after a 6-weeks treatment with acarbose (3x50 mg daily). OGTT after acarbose treatment was not done. The % of sensor glucose levels  $\geq 140$  mg/dl was significantly reduced by treatment with acarbose ( $p=0.046$ , paired t-test). The reduction from baseline in mean 72 hr sensor glucose and maximal daily glucose excursions were not statistically significant.

**Assessor`s comment:**

*Considering that this was a small, short and uncontrolled pilot study, the results are of less importance and are therefore not further described.*

***Published Efficacy of Acarbose in Other Indications***

*Ng D et al.- Acarbose treatment of postprandial hypoglycemia in children after Nissen fundoplication (2001).*

This was an uncontrolled study of 6 children (2 boys, 4 girls) between 4 and 25 months of age.

*Gröbe H and Ullrich K. - Glycogen storage disease Type I. Results of treatment with frequent daytime feeding, combined with nocturnal intragastric feeding and with administration of an  $\alpha$ -glucosidase inhibitor (1983).*

This study investigated the effects of acarbose in 4 children with glycogen storage disease I.

*Hoekstra J et al. Facilitating Effect of Amino Acids on Fructose and Sorbitol Absorption in Children (1996).*

This uncontrolled study investigated the effects of a single, 200 mg dose of acarbose on the intestinal absorption of oral load of 47 g saccharose and of a fructose (25 g)-glucose (27.5 g)-mix in 5 healthy children (2 boys and 3 girls) aged 11.1 to 18.2 years, using breath hydrogen tests.

*Rating D et al. Die Veränderung der Saccharoseresorption nach Acarbose (1982).*

This study investigated the effects of acarbose on the intestinal resorption of saccharose by means of a  $^{13}\text{C}$ -saccharose breath test, in a blinded, placebo-controlled, cross-over design and enrolled 4 children with IDDM, as well as 7 healthy children.

**Assessor`s comment:**

*In the first 3 studies, acarbose is used in a different population than the approved indication for acarbose. In addition they are small and uncontrolled studies, and therefore of limited relevance in this context.*

*The latter small study is regarded an exploratory study, and is not further described.*

In addition to the referred studies, three case reports on the use of acarbose in children were submitted:

*Dura Trave T and Moya Benavent M (1999)* reported on an approximately 9-year-old boy with long-standing reactive postprandial hypoglycaemia.

*Zung A and Zadik Z (2003)* reported on a 12-month-old girl with severe, long-standing dumping syndrome secondary to Nissen fundoplication.

*Yigit S and Estrada E (2002)* reported a case of necrobiosis lipoidica diabetorum associated with venous insufficiency in a 16-year-old, morbidly obese girl.

*Assessor`s comment:*

*3 case reports were submitted. However, only the Yigit and Estrada report included a patient in line with the approved indication. The exact treatment duration of acarbose was not specified, and the role of acarbose on this patient`s clinical course was not commented in the report.*

*The case reports are therefore not focused on in this assessment report.*

### **3. Discussion on clinical aspects**

*Efficacy:*

The submitted documentation comprised 164 paediatric patients exposed to acarbose (including 123 patients with diabetes mellitus), but there is a lack of recent and well-designed paediatric randomised controlled trials. Even though all studies are old and do not comply with the current development guidelines, are often hampered by methodological weaknesses in terms of number of patients and design, the existing data might indicate a small beneficial effect in children with type 1 diabetes mellitus.

As expected, since these studies were performed 20-30 years ago, only type 1 diabetes patients were included. Type 2 diabetes has been recently emerging among – mostly obese - children in puberty. Glucose control deteriorates progressively over time, and after failure of diet and exercise, needs on average a new intervention with glucose-lowering agents every 3-4 years (in adults) to obtain/retain good control. Acarbose has a potential to provide a new treatment option for some children and adolescents with T2DM.

In conclusion, well designed studies examining the efficacy and safety of acarbose in children/adolescents suffering from T1DM or T2DM would have been useful.

*Safety:*

Given the mechanism of action of acarbose, the study population in question (including their background therapy), no new and unexpected adverse events, or pattern of incidences seem to have occurred. The safety profile resembles that in adults, as reflected in the latest agreed Core Safety Profile (ES/H/PSUR/0006/001), and the major adverse events are related to gastrointestinal symptoms. Most studies did not include a titration phase. Slow up titration might have prevented some of the reported GI AEs. Due to the short study duration in most of the studies, it is not known whether these AEs would have declined over time as seen in adults. The reported hypoglycaemic events most likely are considered related to simultaneously insulin therapy.

## **V. DAY 70 RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The MAH conclude that the efficacy and safety of acarbose in patients under 18 years of age have not been adequately investigated.

The Rapporteur agrees with the conclusion of the MAH. The presented paediatric documentation does not fulfill the basic scientific standard required for a change in the SPC labelling.

Beyond the scope of the Article 45 Procedure, acarbose has a potential to provide a new treatment option for some children and adolescents with diabetes. Well designed studies examining the efficacy and safety of acarbose in children and adolescents with T1DM or T2DM would have been useful.

### **➤ Recommendation**

No further action required.

## **VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED**

Glucobay (acarbose) 50 mg tablets, Bayer Schering Pharma AG  
Glucobay (acarbose) 100 mg tablets, Bayer Schering Pharma AG

## **VII DAY 89 CLOCK STOP REQUEST FOR SUPPLEMENTARY INFORMATION**

Following the circulation of the preliminary assessment report on 12 March 2011, comments were received from five member states.

Four member states agreed with the Rapporteur's conclusions and recommendations.

### **Questions received from one MS:**

Even though all studies are old, do not comply with the current development guidelines and are often hampered by methodological weaknesses, the existing data might indicate a small beneficial effect in children with T1DM. In an analogous fashion acarbose might be a treatment option in some children and adolescents with T2DM, a type diabetes that is recently emerging among – mostly obese - children in puberty, although the gastro-intestinal effects could limit the use of this drug.

The aim of Article 45 procedure is to make the information on the use of medicines in the paediatric population available for all health care professionals and patients (or parents).

Therefore MAH is requested to make a proposal for a short description of the paediatric data in section 5.1 and on the safety profile in section 4.8.

## **VIII ASSESSMENT OF RESPONSE TO QUESTIONS**

### **Summary of the MAH's Response**

Based on the recommendation and the comments received from the member states (see section VII) the MAH proposes the following wording to be included in the SmPC:

#### “4.2 Dosage and method of administration (Special populations)

Safety and efficacy of Glucobay in patients under 18 years of age have not been established (see section “Pharmacodynamic properties”).

#### 4.4 Special warnings and precautions for use

Safety and efficacy of Glucobay in patients under 18 years of age have not been established (see “Dosage – Special populations”, “Undesirable effects”, “Pharmacodynamic properties”).

#### 4.8 Undesirable effects

Safety of Glucobay in patients under 18 years of age has not been established (see “Special warnings and precautions for use”, “Dosage-Special populations”, Pharmacodynamic properties”).

#### 5.1 Pharmacodynamic properties

From the review of the efficacy and safety data of 110 paediatric patients exposed to acarbose, in Bayer studies and of over 50 paediatric patients exposed to acarbose in the literature there was no indication of a different mode of action of acarbose in children. The dose administered to the paediatric population was the same as for the adult population. However, the studies and the number of patients are not sufficient to establish efficacy and safety of Glucobay in patients under 18 years of age”.

#### **Assessment of the MAH’s response:**

Although the submitted documentation might indicate some beneficial effect in children with T1DM, one must bear in mind that in general the studies/published articles as well as the paediatric data pool analyses had great limitations including serious flaws in study conduct, small numbers included, lack of control group and lack of significance testing. Taken together, the efficacy and safety results gained from the presented data are considered to be of limited scientific value.

In conclusion, considering that the existing studies quite often are hampered by methodological weaknesses in terms of number of patients, study conduct and design, we do not agree that these data should be added to section 4.4, 4.8 and 5.1 of the SmPC. Inclusion of such information could in our opinion mislead the prescriber. However, the proposed changes to section 4.2 of the SmPC are acceptable.

## **IX MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **Overall conclusion**

In the view of the member states, the presented paediatric documentation does not fulfil the basic scientific standard required for a change in the SmPC labelling of section 4.4, 4.8 and 5.1.

Accordingly, the MAH proposed wording to be included in section 4.4, 4.8 and 5.1 of the SmPC are not supported, while the suggested amendments to section 4.2 are supported to be implemented nationally when applicable.

### **Recommendation**

The member states considers the data on acarbose insufficient to give any advice on paediatric use.

#### Proposed SmPC/PL changes:

If the current SmPC is lacking paediatric information, the following text should be implemented nationally:

“SmPC - Section 4.2

Safety and efficacy of <Product name> in children and adolescents under 18 years of age have not yet been established”.

Chapter 3 of the PL should be amended accordingly.

A Type IB variation on the proposed changes to the SmPC/PL should be submitted by the MAH by 04.10.2011, if not already included.