London, 31 August 2007
Product Name: **Glustin**
Procedure No: **EMEA/H/C/286/II/25**

SCIENTIFIC DISCUSSION

1. INTRODUCTION

Glustin (pioglitazone) is a (2,4) thiazolidinedione derivative that is an orally active ligand for the peroxisome proliferator activated receptor γ (PPARγ). Pioglitazone is currently approved in the EU as monotherapy or in dual oral combination therapy with metformin or a sulphonylurea.

At the time of the original Marketing Authorisation (MA), the Marketing Authorisation Holder (MAH) committed to perform a study investigating the effect of pioglitazone on the total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes. Based on the study results, the MAH applied to extend the current indication to the use of pioglitazone "*as triple oral therapy in combination with metformin and a sulphonylurea, in patients with insufficient glycaemic control despite dual oral therapy*".

In addition, the MAH proposed to delete the following statement in section 4.4: "*There is no clinical experience with pioglitazone in triple combination with other oral antidiabetics*".

2. CLINICAL ASPECTS

The clinical data supporting the proposed extension of indication were collected from a prospective, randomised, double-blind, multicentre, placebo-controlled, parallel-group phase 3b study in patients with type 2 diabetes and pre-existing macrovascular disease (PROactive study or EC444 study). Supportive literature data in relation to the use of triple therapy in the treatment of type 2 diabetes were also provided.

PROactive STUDY DESIGN

Objectives

The primary objective of the study was to demonstrate that pioglitazone reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes.

Study Participants and baseline data

Among the inclusion criteria were:

- Male or female patients, 35 to 75 years.
- Glycosylated haemoglobin above the upper limit of normal (more than 6.5%).
- Established macrovascular disease: myocardial infarction (MI) or stroke at least 6 months before entry, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) at least 6 months before recruitment, acute coronary syndrome(ACS) at least 3 months before recruitment or objective evidence of coronary artery disease (CAD) or lower limb obstructive arterial disease.

Exclusion criteria included Type 1 diabetes; insulin as sole therapy; MI, stroke, CAPG or PCI in the previous 6 months; NYHA functional score of 2 or more; acute coronary syndrome in the previous 3 months.

Treatments

Patients were randomly assigned to receive either pioglitazone or placebo in addition to any existing therapy (including diet and exercise and antidiabetic agents, antihypertensives, lipid-lowering agents, and antithrombotic agents) over a treatment period of 2.5 to 4 years. This was a forced titration study, with the objective of maintaining patients on the maximum tolerated dose of study medication.

All patients in the pioglitazone treatment group began treatment at the 15 mg QD dose and then, based on tolerability, the dose was increased stepwise to 30 mg QD at Visit 2 (Month 1), and 45 mg QD at Visit 3 (Month 2). Throughout the treatment period, the dose could have been increased or decreased

within the range 15 to 45 mg QD as tolerability allowed. Patients returned to the clinical site for follow-up visits at Months 1 and 2, and every 2 months for the remainder of the first year, and then every 3 months for the remainder of the study.

PROactive STUDY BASELINE DATA

In study EC444 (PROactive**)**, approximately one-quarter of all patients (1427 out of the total study population of 5238 patients) received a combination of metformin and sulphonylurea therapy (but no insulin) at study entry to which pioglitazone or placebo was added for up to 3.5 years. This is the cohort of interest for this assessment of the benefit/risk balance of the triple therapy.

The baseline antidiabetic therapy of patients is summarised in table I.

Table I. Baseline Antidiabetic Therapy—EC444: Cohort of Patients Receiving Metformin and Sulphonylurea at Baseline

	Pioglitazone N=711		**Placebo N=716**	
	n (%) (a)	**Total Daily Dose (mg) Mean (SD)**	**n (%)** (a)	**Total Daily Dose (mg) Mean (SD)**
Metformin	701 (98.6)	1675.2 (603.4)	704 (98.3)	1661.2 (633.8)
Sulphonylureas	700 (98.5)		705 (98.5)	
Glibenclamide	226 (31.8)	11.4 (5.0)	203 (28.4)	11.3 (4.8)
Gliclazide	266 (37.4)	188.0 (97.0)	272 (38.0)	182.5 (96.8)
Glimepiride	150 (21.1)	3.4 (1.7)	167 (23.3)	3.5 (1.6)

(a) the baseline Ns exclude those patients on a fixed-dose combination tablet of metformin and sulphonylurea.

Patients in the metformin plus sulphonylurea cohort were receiving mean daily doses of metformin of approximately 1700 mg, which is greater than 50% of the maximum recommended dose. At baseline, most patients (~90%) were receiving glibenclamide, gliclazide, or glimepiride. Approximately 8% of patients within the cohort were receiving an additional non-thiazolidinedione oral agent, most commonly acarbose. The treatment groups were generally similar with respect to baseline antidiabetic therapy.

The mean age was 62 years, approximately two thirds of patients were male, and the nearly entire cohort was Caucasian. The mean duration of disease within the cohort was approximately 9.5 years, virtually the same as for the total study population. Overall, baseline demographic parameters were similar between treatment groups within the cohort and to the total study population.

Similar to the total population, nearly half of the patients in the metformin plus sulphonylurea cohort had a qualifying event of MI and nearly one-fifth a qualifying event of a stroke. Almost half of patients fulfilled 2 or more qualifying entry criteria. A higher proportion of patients (between 3% and 5% treatment-group differential) in the pioglitazone group than in the placebo group had a history of MI, angina pectoris, confirmed coronary artery disease, and PCI, whereas similar rates for a history of hypertension and ACS were noted between treatment groups. The proportion of patients within this cohort receiving specific cardiovascular medications was generally similar to that observed for the total study population.

PROactive STUDY EFFICACY RESULTS

- **Effect on glycaemic control**

Glycaemic controlled was improved from baseline in both treatment groups. The mean change from baseline to final visit in HbA1c (%) is described in table II.

Table II. Mean Change from Baseline in HbA1c (%)—EC444: Cohort of Patients Receiving Metformin and Sulphonylurea at Baseline

	Pioglitazone		Placebo	
Visit, %	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	701	8.2 (1.41)	705	8.2 (1.35)
6 Months	667	-0.83 (1.22)	657	-0.11 (1.23)
12 Months	650	-0.94 (1.18)	653	-0.25 (1.20)
24 Months	623	-0.81 (1.26)	605	-0.15 (1.29)
Final Visit	623	-0.94 (1.29)	613	-0.35 (1.37)

Concomitant anti-diabetes and cardiovascular medications were adjusted as necessary. The change from baseline to the final visit in doses of metformin and sulphonylurea is summarised in table III.

Table III. Change from Baseline to Final Visit in Mean Daily Doses of Metformin and the Most Commonly Used Suphonylurea Agents—EC444: Cohort of Patients Receiving Metformin and Sulphonylurea at Baseline

	Pioglitazone N=711		Placebo N=716	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Metformin Baseline (mg)	701	1675.2 (603.36)	704	1661.2 (633.83)
Change from Baseline to Final Visit (mg)	551	16.0 (563.00)	554	213.3 (618.56)
Sulphonylurea				
Glibenclamide Baseline (mg)	226	11.4 (5.01)	203	11.3 (4.82)
Change from Baseline to Final Visit (mg)	128	-1.3 (3.32)	104	-0.1 (3.46)
Gliclazide Baseline (mg)	266	188.0 (96.99)	272	182.5 (96.78)
Change from Baseline to Final Visit (mg)	180	-32.5 (78.13)	157	-21.6 (91.72)
Glimepiride Baseline (mg)	150	3.4 (1.69)	167	3.5 (1.60)
Change from Baseline to Final Visit (mg)	107	-0.1(1.66)	96	0.6 (1.47)
Glipizide Baseline (mg)	51	11.1 (7.32)	52	10.5 (5.73)
Change from Baseline to Final Visit (mg)	33	-1.9 (6.70)	31	0.9 (4.21)

At the end of the study, approximately 62% of pioglitazone and 55% of placebo patients remained on the metformin plus sulphonylurea therapy. In the pioglitazone group, approximately 14% of patients dropped either metformin or sulphonylurea compared to 7% of placebo-treated patients. Fewer pioglitazone patients had metformin plus sulphonylurea replaced with insulin (5.2% vs 8.4% with placebo). Fewer patients in the pioglitazone group had insulin added to their regimen with or without dropping either metformin or sulphonylurea compared to patients in the placebo group (approximately 10% vs 21%). Within the cohort, nearly equal proportion of patients in either treatment group stopped metformin use (approximately 13%), whereas fewer pioglitazone patients compared to placebo patients stopped sulphonylurea treatment (18% vs 25%).

- **Effect on lipid parameters**

The benefit observed with pioglitazone used as monotherapy and in dual combination therapies on the abnormalities of diabetic dyslipidemia is retrieved in triple combination therapy. The percent decreases from baseline in triglycerides levels (-15%. vs. 8.9%) and increases in HDL-cholesterol (21.6% vs. 13.1%) with pioglitazone were statistically significantly greater than the changes seen in these values with placebo respectively. Both treatment groups had increases in LDL-cholesterol (11.8% vs. 6.6%), however, there was a statistically significant decrease in the LDL-cholesterol/HDL-cholesterol ratio with pioglitazone but not with placebo (-5.1% vs. –2.7%).

PROactive STUDY SAFETY RESULTS

EC444 enrolled more than 5200 patients with long-standing type 2 diabetes mellitus and significant underlying cardiovascular disease. As such, this patient population was at high risk for recurrent cardiovascular events. More than half of the patients within the cohort had a history of pectoris angina and hypertension, while almost half had a history of confirmed ACS and MI.

- **Adverse events (AEs)**

The common AEs (seen at a rate of greater than 1/100, but less than 1/10) observed during study EC444 are summarised in table IV.

Table IV. Common Adverse Events that Occurred Whilst in the Study—EC444: Patients Receiving Metformin and Sulphonylurea at Baseline

SOC Preferred Term	Pioglitazone N=711 n (%)	Placebo N=716 n (%)
Any AE	580 (81.6)	562 (78.5)
Blood and lymphatic system disorders		
Anaemia	21 (3.0)	8 (1.1)
Cardiac disorders		
Cardiac failure	63 (8.9)	42 (5.9)
Myocardial infarction	28 (3.9)	30 (4.2)
Gastrointestinal disorders		
Diarrhoea	36 (5.1)	33 (4.6)
General disorders and administration site conditions		
Chest pain	45 (6.3)	29 (4.1)
Infections and infestations		
Influenza	30 (4.2)	30 (4.2)
Nasopharyngitis	43 (6.0)	65 (9.1)
Injury, poisoning and procedural complications		
Accident	47 (6.6)	27 (3.8)
Musculoskeletal and connective tissue disorders		
Arthralgia	42 (5.9)	53 (7.4)
Back pain	47 (6.6)	45 (6.3)
Pain in extremity	53 (7.5)	43 (6.0)
Nervous system disorders		
Dizziness	30 (4.2)	28 (3.9)
Vascular disorders		
Hypertension	24 (3.4)	38 (5.3)

- **Serious adverse events (SAEs) and fatal adverse events**

The common SAEs for the cohort of patients receiving metformin plus sulphonylurea at baseline are summarised in table V. The most frequently reported SAEs included MI, angina pectoris and cardiac failure. Incidences of the remaining SAEs were generally similar between treatment groups. However, SAEs of cardiac failure, cardiac failure congestive, and pneumonia occurred more frequently in the pioglitazone group, whereas hypertension and hypertensive crisis occurred more frequently in the placebo group.

Table V. Common SAEs Occurring Whilst in the Study—EC444: Patients Receiving Metformin and Sulphonylurea at Baseline

SOC Preferred term	Pioglitazone N=711 n (%)	Placebo N=716 n (%)
Any AE	328 (46.1)	339 (47.3)
Cardiac disorders		
Acute coronary syndrome	4 (0.6)	12 (1.7)
Angina pectoris	25 (3.5)	32 (4.5)
Angina unstable	20 (2.8)	26 (3.6)
Atrial fibrillation	10 (1.4)	12 (1.7)
Cardiac failure	31 (4.4)	21 (2.9)
Cardiac failure congestive	16 (2.3)	8 (1.1)
Myocardial infarction	28 (3.9)	30 (4.2)
General disorders and administration site conditions		
Sudden death	2 (0.3)	7 (1.0)
Infections and infestations		
Osteomyelitis	5 (0.7)	0 (0.0)
Pneumonia	17 (2.4)	8 (1.1)
Injury, poisoning and procedural complications		
Accident	18 (2.5)	9 (1.3)
Nervous system disorders		
Cerebrovascular accident	19 (2.7)	23 (3.2)
Transient ischaemic attack	13 (1.8)	12 (1.7)
Surgical and medical procedures		
Coronary arterial stent insertion	13 (1.8)	8 (1.1)
Coronary artery surgery	15 (2.1)	15 (2.1)
Diabetes mellitus management	15 (2.1)	23 (3.2)
Vascular disorders		
Hypertension	4 (0.6)	11 (1.5)
Hypertensive crisis	1 (0.1)	9 (1.3)
Peripheral vascular disorder	9 (1.3)	4 (0.6)

Fatal SAEs occurring in the cohort of patients of interest are summarised in table VI. In comparison to the overall cohort, in which 6.8% in pioglitazone and 7.1% in placebo groups died, the proportion of patients with fatal SAEs is slightly lower in the metformin plus sulphonylurea group with 5.9% vs. 6.6% for pioglitazone and placebo, respectively. The most common causes of death were cardiac disorders, and the overall incidence was similar between treatment groups. Slightly fewer patients in the pioglitazone group than in the placebo group died from MI or sudden death. Fatal MI and cardiac failure occurred in proportionally fewer patients in the metformin plus sulphonylurea cohort as compared to the total study population.

Table VI. Fatal SAEs Occurring Whilst in the Study that Occurred in at Least To Patients in either Treatment Group—EC444: Patients Receiving Metformin and Sulphonylurea at Baseline

SOC Preferred Term	Pioglitazone N=711 n (%)	Placebo N=716 n (%)
Any event	42 (5.9)	47 (6.6)
Cardiac disorders		
Cardiac arrest	2 (0.3)	1 (0.1)
Cardiac failure	2 (0.3)	3 (0.4)
Cardiac failure congestive	2 (0.3)	0 (0.0)
Myocardial infarction	4 (0.6)	8 (1.1)
General disorders and administration site conditions		
Sudden cardiac death	3 (0.4)	1 (0.1)
Sudden death	2 (0.3)	7 (1.0)
Infections and infestations		
Sepsis	2 (0.3)	1 (0.1)
Neoplasms benign, malignant and unspecified		
Gastric cancer	1 (0.1)	2 (0.3)
Nervous system disorders		
Cerebrovascular accident	2 (0.3)	5 (0.7)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	3 (0.4)	1 (0.1)
Vascular disorders		
Shock	0 (0.0)	2 (0.3)

- **Adverse events of special interest**

Adverse events of hypoglycaemia, oedema, and serious heart failure were considered AEs of special interest in EC444. As such, they were both reported spontaneously by the patient and specifically solicited by the investigator. These AEs of special interest were reported more frequently with pioglitazone than placebo, but the relative risk of each of these events was no different in the cohort metformin plus sulphonylurea to that observed in the total study population (Table VII, VIII and IX).

Table VII. Incidence Rate for Reports of Hypoglycaemia—EC444: Patients Receiving Metformin and Sulphonylurea at Baseline

	Pioglitazone N=711 n (%)	Placebo N=716 n (%)	Risk vs Placebo 95% CI
Patients in the cohort with hypoglycaemia	196 (27.6)	144 (20.1)	1.37 (1.14, 1.65)
Patients in the cohort without hypoglycaemia	515 (72.4)	572 (79.9)	

Table VIII. Incidence Rate for Reports of Oedema—EC444: Patients Receiving Metformin and Sulphonylurea at Baseline

	Pioglitazone N=711 n (%)	Placebo N=716 n (%)	Risk vs Placebo 95% CI
Patients in the cohort with oedema	156 (21.9)	101 (14.4)	1.56 (1.24, 1.95)
Patients in the cohort with no oedema	555 (78.1)	615 (85.9)	

Table IX. Incidence Rate for Reports of Serious Heart Failure—EC444: Patients Receiving Metformin and Sulphonylurea at Baseline

	Pioglitazone N=711 n (%)	Placebo N=716 n (%)	Risk vs Placebo 95% CI
Patients in the cohort with serious heart failure	44 (6.2)	33 (4.6)	1.34 (0.87, 2.08)
Patients in the cohort with without serious heart failure	667 (93.8)	683 (95.4)	

- **Laboratory and other safety findings**

The EC444 study report contains a complete description of the results of laboratory evaluations in the overall study population. No subgroup analyses of laboratory results were done for the population of patients taking metformin plus sulphonylurea combination therapy.
In the overall study population, no deleterious effects on liver function were seen with pioglitazone. Incidences of high ALT, AST, or alkaline phosphatase values were low in both groups, and very few patients in either group had elevations to 3 times the ULN in either variable. Compared with placebo, pioglitazone patients showed a trend toward normalisation of high liver function values from baseline to the Final Visit.
The effects on renal function, as assessed through creatinine measurements, were not distinguishable between pioglitazone and placebo in this study.

Vital Signs, Physical Findings, and Other Observations

The EC444 study report contains a complete description of the results of vital sign evaluations and measurements of weight in the overall study population. Again, no subgroup analyses of the results were done for the population of patients taking metformin plus sulphonylurea combination therapy. In the overall study population, small but consistent decreases were observed from baseline to the final visit in systolic and diastolic blood pressure in both treatment groups. The decreases were slightly greater for pioglitazone than for placebo. Patients in the pioglitazone group gained a mean of 3.8 kg over the 30 months of the study, compared with a mean loss of 0.6 kg for placebo. Most of the weight gain with pioglitazone took place in approximately the first 15 months of the study.

Drug interaction

There was no new drug interaction data derived from the analysis of pioglitazone in oral triple combination therapy. A large number of concomitant medications were given to patients taking part in the clinical trials. No individual drugs or classes of drugs were identified to have any influence on the reported safety profile, and no interactions were reported.

Post marketing surveillance

Cumulative exposure to pioglitazone is estimated to be approximately 3,419,000 patient-years of treatment in the US, 1,175,000 patient-years in Japan and 648,000 patient-years in Europe. In other areas (Canada, South America, African continent, Asian countries, etc.), where patient exposure is estimated, pioglitazone has been prescribed to around 107,000 patients during this period (226,000 patient-years).

The MAH provided an overview of the seven last periodic safety update reports (PSURs). The profile of adverse drug reaction reports in all seven PSURs was consistently similar to that seen in earlier postmarketing reviews and in clinical trials conducted with pioglitazone; thus confirming the known safety profile of pioglitazone.

Reference was also made to an observational study performed on UK-based GPRD (Koro et al) where 21,888 type 2 diabetic patients were identified and a 6:1 nested case-control design was used (1,301 incident CHF cases were identified in the cohort matched to 7,788 controls). After risk factor adjustment, there was a 1.2 fold increase in the risk of CHF for sulphonylureas and metformin monotherapies, a 1.6-fold increase with combination of metformin and sulphonylureas, a 2.2-fold increase for tri-combinations and a 1.5-fold increase for insulin compared to no exposure. Compared to sulphonylureas, bicombinations of metformin and sulphonylureas showed a statistically significant 1.4-fold increase in odds of CHF. The conclusion drawn was that the risk of CHF increased with the complexity of antidiabetic regimen, suggesting that it is diabetes severity which imparts the risk and not necessarily the antidiabetic regimen itself.

Pharmacovigilance and Risk Management Plan

The MAH submitted a risk management plan (RMP). This RMP covers this extension of indication as well as the ongoing EMEA/H/C/268/II/26 (insulin combination indication).

The following table summarises the RMP with regards to the present extension of indication:

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Oedema and heart failure	Routine pharmacovigilance including review in PSURs.	Warning in Section 4.4 of SPC
Hypoglycaemia	Routine pharmacovigilance including review in PSURs.	Warning in Section 4.4 of SPC and listed as ADR in Section 4.8 of the SPC

The CHMP, having considered the data submitted in the application, was of the opinion that no additional risk minimisation activities are required for this particular triple oral therapy extension of indication beyond those included in the product information.

3. OVERALL CONCLUSIONS AND BENEFIT/RISK ASSESSMENT

Glycaemic control was improved with the addition of pioglitazone to metformin and sulphonylurea. The maximum mean decrease in HbA1c was observed at the Month 12 visit, after which it remained stable until the final visit. At all time points, the mean decrease in HbA1c was statistically significantly greater with pioglitazone compared to placebo with a treatment difference in HbA1c of 0.59% at the final visit (-0.94% versus -0.35%, P<0.0001). Fourteen percent of patients did not require or dropped either Metformin or Sulphonylurea compared to 7% of placebo-treated patients. Fewer patients taking pioglitazone progressed to insulin compared with placebo. While an increase in LDL cholesterol with pioglitazone compared to placebo was observed, HDL cholesterol also increased, and the LDL/HDL ratio remained favourable for pioglitazone use.

The mean metformin daily dose at baseline in both treatment groups exceeded 80% of the maximum recommended daily dose of 2000 mg. The mean daily metformin dose at final visit increased by only 213 mg in the placebo group. For glibenclamide, the mean daily dose at baseline exceeded 75% of the maximum recommended daily dose of 15 mg, and there was no increase in the mean daily glibenclamide dose at final visit. The absence of substantial increases in metformin or sulphonylurea and lower proportion of patients requiring initiation of insulin during the study in the pioglitazone group suggest that the patients in the metformin plus sulphonylurea cohort had used the maximum tolerated dose of the dual therapy before being given pioglitazone.

The administration of pioglitazone was generally safe and well tolerated in these high-risk patients who were receiving metformin plus sulphonylurea at study entry who then received pioglitazone.

Higher rates of oedema and heart failure were reported with pioglitazone than with placebo but there is no evidence of increased mortality with long-term pioglitazone treatment. Recent estimates of heart failure rates in type 2 diabetes over a 6-year observation period were as high as 31 per 1,000 person-years compared to a rate of 12 amongst non-diabetic populations (rate ratio 2.5; 95% CI: 2.3,2.7). *Koro et al* (UK based GPRD) concluded from an observational study that the risk of congestive heart failure increased with the complexity of antidiabetic regimen, suggesting that it is the severity of diabetes that imparts the risk and not necessarily the antidiabetic regimen itself. Thus, the incidence of serious heart failure reported in EC444 in the overall population, as well as in the metformin plus sulphonylurea cohort, is within the expected range for patients with type 2 diabetes. Treatment with thiazolidinediones, such as pioglitazone, in patients who are at risk for development of heart failure, should be initiated at the lowest available dose and the dose increased gradually.

A higher rate of hypoglycaemia was reported with pioglitazone than with placebo. This might require a reduction of the dose of the sulphonylurea in patients receiving a triple oral therapy and this has been reflected adequately in the Summary of Product Characteristics (SPC).

A subgroup analysis of all adverse events by the intrinsic factors gender, age, and body mass index was performed on the cohort of patients receiving metformin and sulphonylurea treatment but no insulin at baseline. Overall, the subgroup analysis conducted did not reveal an increased risk of adverse events in relation to gender, age, body mass index with triple therapy use.

Based on the safety and efficacy data provided, the CHMP recommended the extension of indication of Glustin to the use of pioglitazone as triple oral therapy in combination with metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy. Sections 4.1, 4.4 and 4.8 of the SPC as well as the Package Leaflet (PL) were revised accordingly.