EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 19 January 2012
EMEA/CHMP/844031/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pioglitazone Teva

International nonproprietary name: pioglitazone

Procedure No. EMEA/H/C/002297

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1 Background information on the procedure

1.1 Submission of the dossier

The applicant Teva Pharma B.V, submitted on 28 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pioglitazone Teva, through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 February 2010.

The application concerns a generic medicinal product as defined in Article 10(2) (b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

The applicant applied for the following indication:

Pioglitazone Teva is indicated as second or third line treatment of type 2 diabetes mellitus as described below:

as **monotherapy**

- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.

as **dual oral therapy** in combination with

- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

as **triple oral therapy** in combination with

- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC, as amended.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Actos instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Glustin 15 mg, 30 mg Tablets
- Marketing authorisation holder: Takeda Global Research and Development Centre
- Date of authorisation: 13/10/2000
- Marketing authorisation granted by:
  - Community

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Actos 15 mg, 30 mg, 45 mg Tablets

Marketing authorisation holder: Takeda Global Research and Development Centre (Europe)

- Date of authorisation: 13/10/2000
- Marketing authorisation granted by:
  - Community

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Actos 45 mg tablets
- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe)
- Date of authorisation: 16/09/2003
- Marketing authorisation granted by:
  - Community
  - Marketing authorisation number(s): EU/1/00/150/011-015, 022-024, 029-030
  - Member state source: UK
- Bioavailability study number(s): 2010/2349

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.2 Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Patrick Salmon.

- The application was received by the EMA on 28 October 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 February 2011
- During the meeting on 14-17 March 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 March 2011
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 April 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 June 2011
- During the CHMP meeting on 20-23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed by the applicant
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 19 August 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 05 September 2011
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee adopted the CHMP Assessment Report and issued a positive opinion for granting a Marketing Authorisation to Pioglitazone Teva.
- Following the European Commission request from 21 December 2011, the CHMP revised the wording of the product information to ensure that the terms of the marketing authorisation are in line with the outcome of the referral of the reference medicinal product. During the meeting on 16-19 January 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive revised opinion for granting a Marketing Authorisation to Pioglitazone Teva.

2 Scientific discussion

2.1 Introduction

The medicinal product is a generic medicinal product containing pioglitazone as pioglitazone hydrochloride as active substance. The reference medicinal product is Actos 15, 30, 45 mg tablet. Pioglitazone is indicated as second or third line treatment of type 2 diabetes mellitus as described below:

as **monotherapy**

- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.

as **dual oral therapy** in combination with

- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

as **triple oral therapy** in combination with

- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained Pioglitazone is indicated in the treatment of type 2 diabetes mellitus:

Pioglitazone is a high affinity ligand for PPARγ, a member of the nuclear receptor superfamily of ligand-activated transcription factors. The most relevant mode of pioglitazone action seems to be the activation of this receptor. Once activated, PPARγ forms a heterodimer with another nuclear receptor, the retinoid-X receptor. This heterodimer then binds to specific DNA sequences and regulates the transcriptional activity of target genes that play a role in the metabolism of glucose and lipids by regulating synthesis and expression of cellular glucose and fatty acid transporters. Pioglitazone is dependent on the presence of insulin in order to exert its beneficial effects. The activation of PPARγ by pioglitazone leads to increased peripheral, hepatic and adipocyte insulin sensitivity. By reducing insulin resistance, pioglitazone lowers fasting and postprandial blood glucose concentrations, circulating free fatty acids and insulin levels, and also hepatic glucose production may decline.

The glucose-lowering effect of pioglitazone in patients with non-insulin dependent diabetes mellitus is also related to its ability to reduce insulin resistance in skeletal muscle. PPAR- γ activation also

stimulates differentiation of pre-adipocytes and bone marrow stromal cells into mature adipocytes. Barring the beneficial effects on glycaemic control, insulin levels and function and free fatty acids, pioglitazone also confers benefits in terms of other lipid parameters, hsCRP, MMP-9, MCP-1 and adiponectin.

Pioglitazone is indicated for the treatment of non- insulin dependent diabetes mellitus.

It can be prescribed as monotherapy in patients inadequately controlled by diet and exercise in whom metformin is contraindicated or not adequately tolerated.

It can be combined with metformin or sulphonylurea in patients treated with metformin or sulphonylurea drug who have insufficient glycemic control despite maximal tolerated doses of these drugs.

It can be prescribed as a triple combination therapy with metformin and sulphonylurea in patients with insufficient blood sugar control.

Pioglitazone is also indicated for combination with insulin in patients with insufficient glycemic control with insulin.

Pioglitazone is to be taken once daily regardless of food intake. The starting dose may be 15 mg or 30 mg once daily. The maximal daily dose is 45 mg. When the pioglitazone is added on top of insulin, the latter can be continued as previously, while attention has to be paid on hypoglycaemic episodes. If they occur, insulin dose should be reduced.

Pioglitazone can be used in elderly and in patients with impaired renal function (bar dialysis patients) without any dose adjustment. There is a lack of information about the use in dialysis patients therefore pioglitazone should not be used in this patient group.

Pioglitazone is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Cardiac failure or history of cardiac failure (NYHA stages I to IV) is also contraindication for the use of pioglitazone due to increased volume overload as a consequence of fluid retention.

This can exacerbate or trigger heart failure. Therefore pioglitazone has to be administered with caution in patients with any risk factors for heart failure (careful titration and follow up). Pioglitazone must not be administered to patients with hepatic impairment (enzyme ALT > 2.5 times the upper normal limit or any other sign of hepatic disease) due to reports on hepatocelular dysfunction in patients treated with pioglitazone. During the treatment, liver enzymes activity has to be controlled and treatement withdrawn in case of persistent elevations of ALT more than 3 times the normal value.

Pioglitazone is contraindicated in diabetic ketoacidosis.

Pioglitazone is contraindicated in patients with current bladder cancer or a history of bladder cancer, and uninvestigated macroscopic haematuria.

The use of pioglitazone is associated with an increased risk of bone fractures. This risk should be considered in the long term care of women treated with pioglitazone.

2.2 Quality aspects

2.2.1 Introduction

Pioglitazone Teva is presented as tablets containing pioglitazone hydrochloride equivalent to 15 mg, 30 mg and 45 mg of pioglitazone as active substance. The other ingredients are mannitol, carmellose calcium, hydroxypropyl cellulose and magnesium stearate.

The proposed packaging for the finished tablets consists of Aluminium/aluminium blisters placed in a printed carton.

2.2.2 Active Substance

There is no official Pharmacopoeial monograph for pioglitazone hydrochloride, however a draft Pharmeuropa monograph (Vol. 22, No. 4) has been published in October 2010.

This medicinal product contains as active substance pioglitazone as the hydrochloride salt. The chemical name of pioglitazone hydrochloride is (±)-5-[[4-[2-(5-Ethyl-2-pyridinyl)-ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride. The molecular formula is $C_{19}H_{20}N_2O_3S.HCl$ and the molecular weight is 392.90 g/mol.

Pioglitazone is a white to off-white crystalline powder and soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water. Pioglitazone hydrochloride is not hygroscopic active substance. It exhibits stereoisomerism due to the presence of one chiral center and is synthesized and used as racemic mixture. The two enantiomers of pioglitazone inter-convert in vivo. No differences were reported in the pharmacological activity between the two enantiomers.

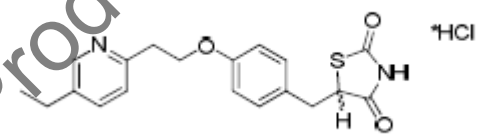


Figure 1: pioglitazone hydrochloride

Manufacture

Information about the manufacturing process has been provided using two Active Substance Master File (ASMF) procedures. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of two active substance master files (ASMF). In one of manufacturing processes the active substance is synthesised in 4 steps and in the third step two routes of synthesis were considered. In other manufacturing processes the active substance is synthesised in 4 steps, but in the second step two alternatives routes of synthesis were described. In the last step of both manufacturing processes the purification of the active

substance is done by crystallisation. The purified active substance is packed into clear LDPE bags, purged with nitrogen and tied. The clear bag is placed inside black polythene bag with silica gel bag and tied. This double polythene bag pack is placed inside a triple laminated bag and sealed with sealer and kept in HDPE container with a HDPE lid and this outer container is also sealed with tamper evident seal. The purified active substance can also be packed into an LDPE bag cable tied and places into an outer aluminium laminated bag which is heat sealed and introduced into an outer HDPE container.

The chemical structure of the active substance has been confirmed by spectroscopy FTIR, ^{1}H-NMR, ^{13}C-NMR, and MS). In addition the molecular weight was determined by elemental analysis.

Specification

There is no Ph.Eur monograph for pioglitazone hydrochloride and hence the active substance is tested as per in-house specifications. The active substance manufactureres' specifications include tests for appearance, identification (IR & HPLC), identification of chloride (Ph. Eur.), XRD, loss on drying, solubility, optical rotation (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), assay (HPLC), impurities (HPLC), palladium content, particle size, bulk density, tapped density and residual solvents (GC). A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general, the analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data of five batches of active substance are provided. The tests and limits in the specifications are considered appropriates for controlling the quality of this active substance.

Stability

Stability results from long-term (25°C/60%RH) and accelerated studies (40°C/75%RH) for four production scale batches, which include one route of synthesis, and five other production scale batches, which are represented from other route of synthesis, were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: appearance, identification (IR & HPLC), XRD, water content, impurities (HPLC) and assay (HPLC).It was noticed that the test methods applied are those used for release of the active substance. A photostability testing programme was conducted in accordance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications and the finished product does not require any special light protection since this active substance is photostable. In can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packing material.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate a conventional immediate-release tablet containing qualitatively and quantitatively the same active substance as the originator products Actos and Glustin (which are identical duplicate products marketed by Takeda) and exhibiting the same bioavailability. A common formulation and manufacturing process was developed for all 3 strengths. It was noted that most of the excipients of this new generic medicinal product are common to the

reference product. All excipients selected for this formulation are commonly used in pharmaceutical formulations. During the pharmaceutical development critical formulation and manufacturing parameters were identified and adjusted. The comparative dissolution profiles were provided for all strengths. The results demonstrated that the generic batches used for the bioequivalence studies and the EU brand leader batches are similar with respect to dissolution rate.

Manufacture of the product

The proposed commercial manufacturing process for the tablets involves standard technology and it is divided into the following steps: mixing, granulation, drying, milling, blending, compression and packaging. The equipment used is commonly available in the pharmaceutical industry. The manufacturing process has been adequately described and some steps have been identified as critical and optimised during the drug development (granulation and compression of tablets). The manufacturing process has been adequately validated for two pilot scale batches per strength per manufacturer of the active substance. Furthermore, the validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identification (HPLC & UV), assay (HPLC), dissolution, uniformity of dosage (Ph.Eur), impurities (HPLC), microbiological purity (Ph.Eur), water content, average weight, individual weight, thickness, dimensions, friability (Ph.Eur) and resistance to crushing of tablets (Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. No impurities are caused by the interaction with the excipients used in the formulation. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for two pilot batches per manufacture of the active substance confirm that the tablets can be manufactured reproducibly according to the agreed finished product specifications.

Stability of the product

Stability results from long-term (25°C/60%RH) and accelerated studies (40°C/75%RH) for two pilot scales batches per strength and per active substance supplier were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: assay, related substances, dissolution, water content, appearance and description and microbiological quality. It was noted that the test methods applied are those used for release of the finished product. All the results remained well within the specification limits during all the stability studies. For bulk storage (LDPE bags with desiccants) studies were performed at ICH long term conditions (25°C/ 60%RH) for 1 pilot batch per active substance supplier, per strength. A photostability testing programme was conducted in accordance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications and the finished product does not require any special light protection. Forced degradation test were performed under sunlight, heat, hydrolysis, acidic, basic, and oxidative conditions. Based on the results, it was noted that these stress conditions have shown that only exposure of the finished product to highly extreme condition of adding strong base with heating may cause degradation. Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4 Discussion on chemical, and pharmaceutical aspects

There is no official Pharmacopoeial monograph for pioglitazone hydrochloride, however a draft Pharmeuropa monograph (Vol. 22, No. 4) has been published in October 2010.

The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated for four the pilot scale batches per strength. Furthermore, the validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing. The routine specifications and tests methods proposed for the active substance and finished product will adequately control the quality of the active substance and finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure system was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for finished were adequately established.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished products have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, all quality issues have been resolved.

2.2.6 Recommendation(s) for future quality development

None

2.3 Non- Clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product, Actos, which has been authorised for 10 years.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.1 Ecotoxicity/environmental risk assessment

An environmental risk assessment has been conducted. The ERA is dated July 2010 and concludes that since this is a generic product there will be no increase in environmental exposure to Pioglitazone hydrochloride following marketing authorisation. This was accepted by the CHMP.

2.4 Clinical Aspects

2.4.1 Introduction

This is an application for tablets containing pioglitazone hydrochloride. To support the marketing authorisation application the applicant conducted a single bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A bioequivalence study using the 45mg dose has been carried out. The 45 mg strength was chosen because it is the largest dose, the conditions for a biowaiver for the 15 and 30 mg doses have been met in accordance with the current bioequivalence guideline apart from the fact that the applicant does not mention whether the pharmacokinetics are linear or not. A justification for the strength used is given in the overview of the Clinical Expert namely that the following general requirements for waiver for additional strengths are met:

a) the pharmaceutical products are manufactured by the same manufacturing process;

b) the qualitative composition of the different strengths is the same;

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths;

d) appropriate in vitro dissolution data….”

Therefore, a biowaiver for the lower doses was acceptable.

Clinical studies

A single bioequivalence study has been submitted in support of the application.

2.4.2 Pharmacokinetics

Methods

Study design

A single bioequivalence study was carried out in Canada in March 2010 in 42 healthy males and females aged over 18 years.

The study was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover study, designed to evaluate the comparative bioavailability between two formulations of pioglitazone HCl tablets administered to healthy male and female subjects under fasting conditions.

The washout period between receiving the test and reference product or vice versa was 13 days and 23 hours (14 days in the protocol). The half life of piaglitazone is described as being from 3 to 7 hours and its metabolite from 16 to 24 hours. The test and reference products were administered after an overnight fast of at least 10 hours and subjects continued to fast for at least 4 hours following drug administration. Study drugs were administered with 150 mL of ≈ 25% glucose solution. Subjects also received an additional 100 mL of 25% glucose solution at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 7 hours post-dose (±10 minutes). The investigator reserved the right to alter the glucose administration schedule, discontinue glucose administration, or administer extra glucose solution for any individual subject as necessary. 200 mL of apple juice may have been substituted for the 25% glucose solution at any time except at dosing and within 1 hour after dosing.

In each period, 24 blood samples from 23 time points were obtained from an arm vein of each subject by direct venipuncture or from an indwelling cannula. Blood was collected prior to drug administration and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours following drug administration.

The analytical personnel were blinded from the treatment sequence throughout the analytical process.

Test and reference products

The test product was Pioglitazone hydrochloride 45 mg tablets (Teva Pharmaceuticals Ltd.); Batch No.: K-43813. The reference product was Actos 45mg tablets (Takeda Global Research and Development Centre (Europe) Ltd., UK); Batch No.: 4250008B.

Population studied

Forty-two healthy males and females aged 18 years or older, with a BMI in the normal or overweight category, with no clinically significantly abnormal findings on laboratory examination, ECG examination or vital sign measurements and who did not meet any of the exclusion criteria. One subject withdrew from the study prior to Period 2 check-in due to personal reasons. A sample size calculation estimated that 36 subjects were required (assuming an intra-subject variability of for pioglitazone Cmax of 25% and a difference between the treatment means of ≤ 5%) to ensure a 90% probability of the 90% confidence interval of the treatment mean ratio to be within the 80-125% range. Six further subjects were included in the study to account for dropouts.

Of the 41 subjects who were included in the data analysis, 20 were White, 11 were Hispanic/Latino, 6 were Asian and 4 were Black. Twenty-two (22) subjects were male and 19 were female.

Analytical methods

Subject plasma concentrations of pioglitazone were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) method) developed by a bioanalytical laboratory. The method involved protein precipitation. Sample analysis was conducted using reversed phase chromatography. The method was GLP compliant.

Pharmacokinetic Variables

The following pharmacokinetic parameters were estimated based on pioglitazone levels for each subject in the dataset: AUC 0-t, AUC 0-∞, Cmax, Tmax, Kel and T1/2 The pharmacokinetic variables chosen were considered appropriate by the CHMP.

Statistical methods

Analysis of variance (ANOVA) was applied to log-transformed AUC0-t, AUC0-inf, and Cmax parameters. The significance of the sequence, period, treatment, and subject-within-sequence effects were tested.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means, and the corresponding standard errors of these differences were estimated for log-transformed AUC0-t, AUC0-∞, and Cmax parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

Based on the log-transformed parameters, the following criteria was used to evaluate the bioequivalence between the test and reference products. The 90% confidence intervals of the relative mean AUC0-t and Cmax of the test to reference products should be between 80.00% and 125.00%.

One subject withdrew from the study and was not replaced. Another subject vomited within 5 minutes of the first dose, was withdrawn from the study and subsequently replaced (contrary to the protocol). The pharmacokinetic and statistical analysis was performed on data from a total of 41 subjects. A missing value was used in the pharmacokinetic analysis of pioglitazone concentration levels corresponding to the following sample that was not collected. There were a number of protocol deviations including some late blood samplings. However for the latter, actual study sampling time rather than planned time was used in the PK analysis. Overall the protocol deviations were considered unlikely to have impacted on the study results by CHMP.

Results

41 participants were included in the PK dataset.

Results for arithmetic and geometric means of AUC 0-t, AUC 0-∞ and Cmax and arithmetic means of Tmax, Kel and T1/2 are shown in the following table.

The ratios of the geometric means and the corresponding 90% confidence intervals (test versus reference) for AUCt, AUC∞ and Cmax were as follows [mean (CI)]:

AUC0-t: 101.67% (96.57 - 107.04%)

AUC0-∞: 101.60% (96.57 - 106.89%)

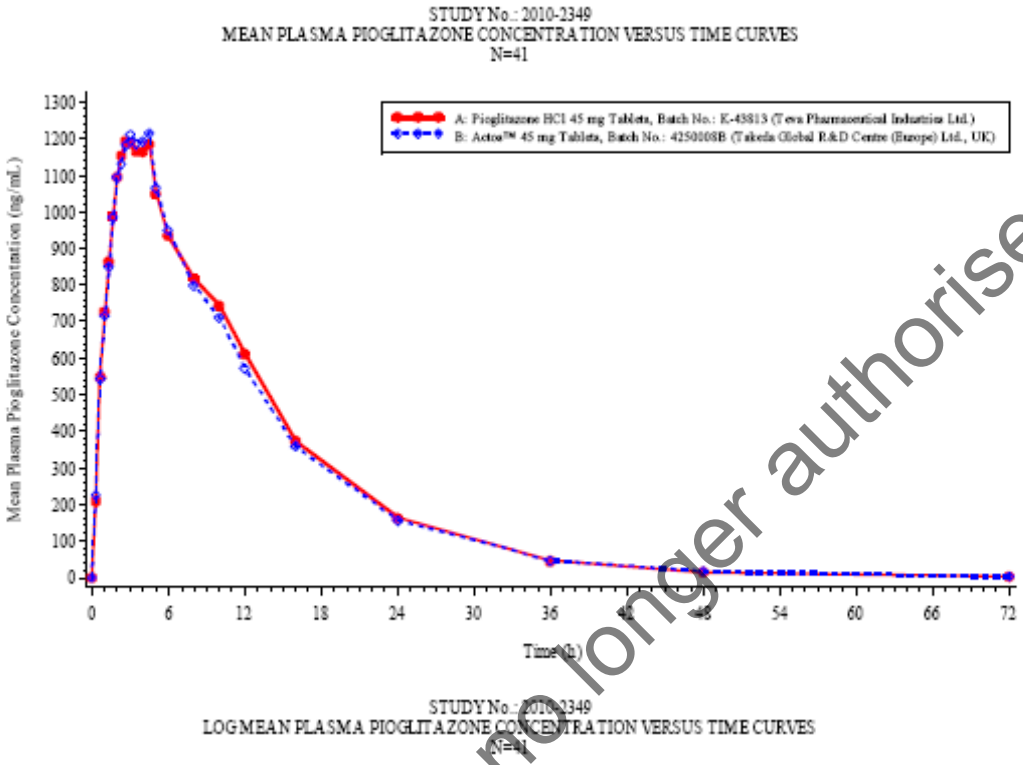
Cmax: 101.03% (93.75 - 108.87%)

The arithmetic means Tmax values were 4.52 hours and 4.09 hours for the test and reference products, respectively. ANOVA did not detect a significant difference in any of the pharmacokinetic parameters.

Table 1: Summary of results:

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic	(CV%)	Geometric			Lower	Upper	
Based on Measured Data									
AUC_{0-t}	A	16335.45	(28)	15705.83	A vs. B	101.67	96.57	- 107.04	14
(ng·h/mL)	B	16052.97	(28)	15448.21					
AUC_{0-inf}	A	16428.77	(27)	15802.77	A vs. B	101.60	96.57	- 106.89	14
(ng·h/mL)	B	16168.10	(28)	15554.03					
Cmax	A	1342.90	(37)	1240.56	A vs. B	101.03	93.75	- 108.87	20
(ng/mL)	B	1321.59	(35)	1227.92					
Tmax	A	4.52	(61)						
(h)	B	4.09	(51)						
Kel	A	0.0948	(34)						
(1/h)	B	0.1013	(30)						
Thalf	A	8.42	(45)						
(h)	B	7.66	(39)						

Figure 2: Mean pioglitazone concentration time curves for Pioglitazone Teva and Actos:



Conclusion: As the 90% confidence intervals for the ratios of the test to reference product geometric means of AUC0-t, and Cmax lie between 80% and 125% bioequivalence between Pioglitazone hydrochloride (Teva) and Actos (Takeda) can be assumed.

Safety data

There were 60 adverse events involving 23 subjects in the study. All adverse events were categorised as mild. Most adverse events occurred only once. Four of those receiving product A had headache, 5 hyperglycaemia, 3 blood urine present and 2 red blood cell urine positive. Of those receiving treatment B, 4 had catheter site pain, 3 had dizziness and 2 hyperglycaemia.

Conclusions

Based on the presented bioequivalence study Pioglitazone Teva is considered bioequivalent with Actos.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4 Additional data

None

2.4.5 Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.6 Discussion on Clinical aspects

A single GCP-compliant open-label, single-dose, randomized, crossover study bioequivalence study was carried out in 42 healthy males and females aged over 18 years. Overall, the design of the trial and the analytical methods used were adequate. Protocol violations were considered to be minor. The ratios of the geometric means and the corresponding 90% confidence intervals (test versus reference) for AUCt, AUC∞ and Cmax were used to demonstrate bioequivalence. The pre-set bioequivalence criteria were met.

2.4.7 Conclusions on clinical aspects

Bioequivalence between Pioglitazone Teva and Actos has been demonstrated as the 90% confidence intervals for the ratios of the test to reference product geometric means of AUC0-t, and Cmax were found to lie between 80% and 125%.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant did not submit a risk management plan because this application concerns a generic for a reference medicinal product for which no safety concern requiring additional risk minimisation activities had been identified when the Marketing Authorisation application was submitted. However taking into account the outcome of the Article 20 procedure on already authorised pioglitazone containing products and the potential increased risk of bladder cancer, the MAH shall submit within one month of the Commission Decision a risk management plan which will incorporate risk minimisation measures, as detailed in the conditions or restrictions with regard to the safe and effective use of the medicinal product in Annex II, in line with those required for the reference medicinal product.

The MAH shall perform the Pharmacovigilance activities detailed in the Pharmacovigilance Plan, to be agreed in the Risk Management Plan to be submitted and any consequent updates to the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal product for human use, the updated RMP should be submitted at the same time as the next PSUR.

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (Pharmacovigilance or risk minimisation) milestone being reached

- At the request of the European Medicines Agency

PSUR submission

The PSUR cycle for the product will follow the PSUR submission schedule of the reference medicinal product, which is on a 6 monthly cycle, having 1 February 2012 as its data lock point.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3 Benefit-Risk Balance

This application concerns a generic version of pioglitazone tablets. The reference product Actos is indicated as second or third line treatment of type 2 diabetes mellitus. No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, single-dose, randomized, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pioglitazone Teva met the protocol-defined criteria for bioequivalence when compared with Actos. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80 to 125%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application, the available data on the chosen reference medicinal product and the outcome of the Article 20 procedure on the already authorised pioglitazone containing products and the potential increased risk of bladder cancer, is of the opinion that additional risk minimisation activities are required beyond those included in the product information as per the conditions of the Marketing Authorisation included in Annex II.

4 Recommendation

Based on the CHMP review of data on quality, safety and efficacy and taking into account the opinions adopted by the CHMP on 21 July 2011 and 20 October 2011 in the framework of the procedures under Article 20 of Regulation 726/2004 for pioglitazone containing medicinal products and the subsequent Commission Decision, the CHMP considers by majority that the risk-benefit balance of Pioglitazone Teva is favourable as second or third line treatment of type 2 diabetes mellitus as described below:

as monotherapy in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance;

as dual oral therapy in combination with
- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin;
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea;

as triple oral therapy in combination with
- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH shall submit within one month of the Commission Decision a risk management plan which will incorporate risk minimisation measures, as detailed below, in line with those required for the reference medicinal product.

The MAH shall perform the Pharmacovigilance activities detailed in the Pharmacovigilance Plan, to be agreed in the Risk Management Plan to be submitted and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (Pharmacovigilance or risk minimisation) milestone being reached

- At the request of the European Medicines Agency

The PSUR submission schedule should follow the PSUR submission schedule of the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use Pioglitazone. Prior to distribution of the prescriber guide in each Member State, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

- This educational pack is aimed at strengthening awareness of important identified risks of bladder cancer and heart failure and the overall recommendations intended to optimise the benefit-risk margin at the patient level.
- The physician educational pack should contain: The Summary of Product Characteristics, package leaflet, and a Prescriber Guide.

The Prescriber Guide should highlight the following:

- Patient selection criteria including that Pioglitazone should not be used as first line therapy and emphasising the need for regular review of treatment benefit.
- The risk of bladder cancer and relevant risk minimisation advice.
- The risk of heart failure and relevant risk minimisation advice.
- Caution in use in the elderly in light of age related risks (in particular bladder cancer, fractures and heart failure).

Divergent positions are appended to this report.

Appendix I

Divergent positions

Divergent statement

We have a divergent position from the above mentioned positive opinion recommending granting of Marketing Authorisation from that which has been readopted by the CHMP during its January 2012 session:

We consider that the benefit-risk balance of pioglitazone has become negative given the increased risk of bladder cancer in addition to the other well known adverse effects (especially heart failure and bone fracture in post menopausal women) of this medicine, its questionable long term benefit in terms of cardiovascular protection and the available alternative treatments in type 2 diabetic patients.

1. Pre-clinical data indicate an increased frequency of bladder cancer associated with pioglitazone in male rats. Results of the PROactive trial show a significantly higher number of bladder cancer in patients treated with pioglitazone. Data provided by three epidemiologic studies (US, France and UK) provide very similar evidence of an increased risk of bladder cancer, even though the magnitude of such risk is low with a hazard ratio around 1.2, however, likely increasing with cumulative dose and duration of pioglitazone exposure.
2. This increased risk of bladder cancer includes invasive types of bladder cancer with major adverse impact on morbidity and mortality. No biomarker of bladder cancer is available which could provide effective screening and early treatment. Symptoms such as haematuria can occur late after the onset of tumour development and are not specific. Cystoscopy appears to be the only investigational procedure able to adequately establish the diagnosis of bladder cancer but its invasive nature precludes is use for systematic cancer screening.

It appears impossible to define a subpopulation of diabetic patients where the benefits of pioglitazone would outweigh its risks. In addition, according to Proactive long term follow up and utilisation studies, a large proportion of patients stop pioglitazone treatment within the first years of treatment precluding potential long term benefit on prevention of cardiovascular events. The identified increased bladder cancer risk is likely to reduce adherence to pioglitazone long term treatment.

CHMP members expressing a divergent opinion:

Pierre Demolis (FR)	19 January 2012	Signature: ……
Harald Enzmann (DE)	19 January 2012	Signature: ……
Nela Vilceanu (RO)	19 January 2012	Signature: ……