EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 January 2012
EMA/CHMP/46573/2012

Assessment report

Pioglitazone Accord

International non proprietary name: Pioglitazone

Procedure No. EMEA/H/C/2277

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 Accord Healthcare Limited submitted on 28 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pioglitazone Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 January 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 Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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

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.

The application submitted is composed of administrative information, complete quality data and a bioequivalence 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: Actos, 15, 30, 45 mg tablet
  - Marketing authorisation holder: Takeda Global Research and Development Centre (Europe), Ltd.
  - Date of authorisation: 13 October 2000
  - Marketing authorisation granted by:
    - Community
      - Community Marketing authorisation numbers: EU/1/00/150/001-030

■ 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, 30, 45 mg tablet
- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe), Ltd.
- Date of authorisation: 13 October 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 tablet
- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe), Ltd.
- Date of authorisation: 13 October 2010
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/00/150/012
- Bioavailability study number: 068-05

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.

1.2 Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team was:

Rapporteur: P. 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 10 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 7 June 2011.
- During the CHMP meeting on 20-23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 28 June 2011.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 July 2011.
- During the meeting on 18-21 July 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 HCL Accord.
- 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 authorization is in line with the outcome of the referral of the reference medicinal products. 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 HCL Accord.

2 Scientific discussion

2.1 Introduction

The 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 a thiazolidinedione compound that acts as a peroxisome proliferator activating receptor (PPAR)-γ agonist with potential benefits on insulin resistance. Pioglitazone has a different mechanism of action compared to other drugs. It does not stimulate insulin secretion (unlike sulphonylureas), and it does not inhibit glucose absorption (unlike alpha -glucosidase inhibitors). It depends on the presence of insulin for activity.

The safety and efficacy profile of pioglitazone has been demonstrated in several clinical trials details of which can be found in the EPAR for Actos. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Actos, summary of the clinical data of pioglitazone hydrichloride is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Pioglitazone Accord 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.

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.

2.2 Quality aspects

2.2.1 Introduction

The product is presented as tablets containing 15, 30 and 45 mg of pioglitazone hydrochloride as active substance.
Other ingredients are carmellose calcium, hydroxypropyl cellulose, lactose monohydrate , and magnesium stearate

The tablets are packed in Aluminium/aluminium blisters.

2.2.2 Active Substance

This medicinal product contains as active substance pioglitazone INN, as the hydrochloride. 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 hydrochloride appears as a white to off-white crystalline powder and is practically insoluble in water and ether. The solubility is highly pH dependent and is greater at lower pH. The active substance is soluble in dimethyl formamide, slightly soluble in anhydrous ethanol and very slightly soluble in acetone and acetonitrile.

Pioglitazone hydrochloride is not hygroscopic. 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.

Pioglitazone hydrochloride exists at least in two different crystal forms, referred to as polymorph I and polymorph II. Polymorph I is routinely produced by the synthetic process described in the dossier and is used in the manufacture of the finished product.

Manufacture

At the time of the CHMP opinion, the active substance used for Pioglitazone Accord is supplied by one active substance manufacturer. Because no Ph.Eur. certificate of suitability has been issued for the active substance manufactured by the proposed supplier, 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 an active substance master file (ASMF). The manufacturing process consists of six steps. The last step, pioglitazone base is purified and treated with HCl to yield pioglitazone hydrochloride. All manufacturing steps are adequately described. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized. The applicant confirmed the structure of the pioglitazone hydrochloride by IR, ^{1}H NMR, ^{13}C NMR, MS and UV. The crystalline nature and polymorphism were characterised by DSC and XRD.

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 manufacturer's specifications include tests as: description, solubility, identification (IR, test for chloride), loss on drying, residue on ignition, heavy metals (Ph.Eur), melting range, related substances (HPLC), assay (HPLC), residual solvents (GC), dimethyl formamide and methyl acrylate content (GC) and nickel content (AAS).

The specifications and tests proposed are compliant with the relevant ICH guidelines and general requirements of Ph.Eur. The specifications are adequate 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 have been provided by the active substance supplier on six batches. All batches were in compliance with the predefined active substance specifications and confirm consistency and uniformity of the active substance manufacture)

Stability

Pioglitazone hydrochloride powder is stored in clear LDPE bags placed in a HDPE container. A silica gel sachet is placed between the inner and outer LDPE bag. Specifications, testing methods and certificates of analysis have been provided for the packaging materials and the silica gel sachet. The LDPE bags comply with Directive 2002/72/EC and Ph.Eur. and are safe for use in contact with food stuffs and pharmaceuticals. The container closure system is described in sufficient detail and the packaging materials are acceptable.

Stability studies on the active substance have been performed at long term (25±2°C/60±5% RH) and accelerated (40±2°C/75±5% RH) conditions on six process validation batches as per ICH Guidelines. Up to 60 months of long term stability data, and up to 6 months of accelerated stability data has been provided, confirming the stability of the active substance. The specifications tested were description, identification (IR), XRD, loss on drying, related substances and assay (HPLC). The HPLC method used for assay and related substances demonstrated to be stability indicating. The packaging used in stability trials is identical to that proposed for storage and distribution.

Forced degradation studies have been performed on one batch. Samples were exposed to UV radiation, heat (60°C and 105°C), atmosphere (25°C/60%RH for 72 hours), humidity (25°C/90% RH for 72 hours), acid hydrolysis, base hydrolysis and peroxide oxidation and analyzed for appearance, identity by IR, XRD, assay, related substances and hygroscopicity. The study revealed that exposure to heat (105°C) results in a change in appearance and that exposure to heat and UV light results in a slight drop (1.5%-2%) in assay. Degradation occurs when exposed to 0.1N NaOH and a slight increase of total impurities was seen after exposure to heat (105°C) and peroxide. No considerable degradation occurs at the other conditions. The hygroscopic nature was tested in accordance with the Ph.Eur. showing that the drug substance is non-hygroscopic.

The stability data provided support the proposed retest period at the proposed packaging and storage conditions.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The aim of the product development was to formulate tablets which are robust, stable and are bioequivalent to the reference medical product. The dissolution data reveals that the dissolution pattern of the test product is matching with that of reference medicinal product for each strengths and the test product 15mg & 30mg are comparable to that of test product 45mg on which BE study has been conducted.
A number of studies were also carried out to define the compatibility of the active substance with the pharmaceutical excipients used.. The manufacturing process development was clearly outlined; the final manufacturing method chosen was standard wet granulation

The excipients used in the formulation are the same as those used in the reference medicinal product. All excipients are stated to comply with the latest edition of the European Pharmacopoeia. Sample certificates of analysis of excipients were provided.

The product is packaged in aluminium-aluminium blister packs; the forming foil is cold formable, Alu-Alu, triple laminated foil and the lidding foil is plain aluminium foil.
Specification for the triple-laminated, cold formable forming foil and the plain aluminium lidding foil are provided, along with representative certificates of analysis. Certificates confirm compliance with relevant EU directives (78/142/EEC, 2002/72/EC) and European Pharmacopoeia requirements .

Adventitious agents

The lactose anhydrous is derived from milk, it is declared that it satisfy the requirements outlined in the TSE Guideline.

Manufacture of the product

The manufacturing process includes dry mixing, granulation, blending, and compression.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process.
The batch analysis data show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product Specification

The finished product specifications include appropriate tests for description, average weight of tablet, resistance to crushing (Ph Eur), friability (Ph Eur), identification (HPLC, UV, Chloride), dissolution, related substance (HPLC), uniformity (Ph Eur), assay (95.0% - 105.0%, HPLC), microbiological quality (Ph Eur).

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are qualified and justified by toxicology studies

Stability of the product

Stability studies were provided on six pilot scale batches carried out in accordance with current ICH/CHMP guidelines and the characteristics tested were as presented in the finished product specifications. Based on the stability data submitted the proposed shelf life of 4 years for the 30 mg and 45 mg strengths and 3 years for 15 mg strength with no storage precautions for the finished product as packaged for sale and 6 months for the bulk product..

2.2.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product 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 product should have a satisfactory and uniform performance in the clinic.'

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6 Recommendation(s) for future quality development

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. The impurity profile has been discussed and was considered acceptable.

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

Ecotoxicity/environmental risk assessment

The introduction of Pioglitazone Accord in the market is considered unlikely to result in any significant increase in the combined sales volumes for all pioglitazone containing products and would thus not be expected to have an adverse effect upon the environment. With this regards and on the basis of CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00), a formal environmental risk assessment is not considered necessary.

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 one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

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

Clinical studies

To support the application, the applicant has submitted one bioequivalence study to demonstrate bioequivalence between their product and the reference product Actos. This pivotal study was an open label, balanced, randomised, two-treatment, two period, two-sequence cross over, single oral dose, bioequivalence study of two formulations of pioglitazone hydrochloride tablets 45 mg in healthy, adult, human male subjects under fasting conditions.

An acceptable request for a waiver of bio-study on the remaining strengths (i.e. 15 mg and 30 mg tablets) was submitted and was based on the following justifications:

1. All the strengths are manufactured at the same site using a similar manufacturing process.
2. The qualitative composition of 15mg, 30mg and 45mg formulation is same.
3. The composition of the strengths is quantitatively proportional.
4. Dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.
5. Pioglitazone demonstrates linear pharmacokinetics.

2.4.2 Pharmacokinetics

Methods

Study design

Study code: 068-05

Title of the study: A two-way crossover comparative evaluation of relative bioavailabilities of two formulations of pioglitazone tablets 45mg in healthy human male subjects under fasting conditions.

The study was an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover comparative oral bioavailability study in healthy, adult male human subjects under fasting conditions. The aim of the study was to evaluate the bioavailability and to assess the bioequivalence of the sponsor's formulation in comparison with the reference formulation. To establish this, a single dose fasting study in healthy male human subjects was planned based on CHMP guidance.

The plasma samples obtained from 48 subjects who completed the study and those withdrawn on medical grounds, were to be analysed for pioglitazone and its M4 metabolite.

The mean serum half-life of pioglitazone and total pioglitazone (pioglitazone + metabolite) ranges from 3 to 7 hours and 16 to 24 hours respectively as reported in the literature. Based on the half life a washout period of 15 days was considered to be adequate.

Pharmacokinetic parameters for both the test and reference formulations were estimated from the plasma drug concentrations of pioglitazone and M4 metabolite. Parametric 90% CI for the ratio of the geometric least squares mean of the calculated pharmacokinetic parameters, Cmax, AUCo-t, and AUC0-inf of the two drug formulations were to be computed for pioglitazone. Only descriptive statistics was to be calculated and reported for M4 metabolite.

Test and reference products

Test Product: Pioglitazone hydrochloride tablets 45 mg (Intas pharmaceuticals ltd)
Batch Number: F2333

Reference Product: ACTOS 45 mg tablets (Pioglitazone hydrochloride tablets 45 mg) manufactured by Takeda Europe R&D Center UK.
Batch Number: 35018A

Population(s) studied

A total of 53 (including 2 standby) healthy, adult male volunteers, aged 18-55 years and with Body Mass index (BMI) 18.5-24.9 kg/m2 were included in the study. These were medically healthy subjects with clinically normal laboratory profiles, vital signs, ECGs and X-ray recordings. Of the 53 subjects, 3 were withdrawn from the trial on medical grounds on the day of check-in for Period-I and were replaced by 3 other subjects.

Thus, 50 subjects were to be dosed. Plasma samples of 48 subjects were obtained (46 subjects who completed the study successfully) and 2 subjects who were withdrawn on medical grounds.

Analytical methods

The plasma samples of subjects were to be analysed using a validated Liquid chromatography–Tandem mass spectrometry (LC-MS / MS) method at the Bioanalytical facility of Lambda Therapeutic Research Ltd., Ahmedabad. The method validation report was provided by the applicant. Calibration curves using 8-point calibration curve standards for pioglitazone and M4 metabolite with concentration ranging from 15.186 ng / mL to 1983.197 ng / mL and 10.206 ng / mL to 989.760 ng / mL respectively were used to determine the concentration of pioglitazone and M4 metabolite in the samples of various subjects.

Pharmacokinetic Variables

As the objective of the study was to compare the bioavailability and characterise the pharmacokinetic profile of the two formulations of pioglitazone and to assess the bioequivalence of pioglitazone, the following pharmacokinetic parameters were to be calculated: Tmax, Cmax, AUCo-t, AUCo-inf and t ½.

Statistical methods

The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartimental model using WinNonlin Professional Software Version 4.1 (Pharsight Corporation, USA) for pioglitazone and M4 metabolite independently. Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC MIXED of SAS Version 9.1 (SAS Institute Inc, USA) to assess the bioequivalence of pioglitazone. Only descriptive statistics was carried out and reported for M4 metabolite.

The statistical methods were acceptable.

Results

The results for the pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median) and for the mean ratios of the 90%CI for AUC0-t, AUC0-inf, Cmax are summarised in the tables below.

Table 1: Descriptive Statistics of Formulation Means for pioglitazone (N=46)

Parameters (Units)	Mean ± SD (Untransformed data)	
	Reference Product-A	Test Product-B
T_{max} (h)	1.833 ± 0.9566	1.895 ± 1.0632
C_{max} (ng/mL)	1463.267 ± 558.7813	1391.352 ± 437.6264
AUC_{0-t} (ng.h/mL)	13014.911 ± 5515.1856	12727.578 ± 4525.9714
$AUC_{0-\infty}$ (ng.h/mL)	13664.014 ± 5787.7319	13200.452 ± 4715.0547
λ_z (1/h)	0.0970 ± 0.02941	0.0960 ± 0.02982
$t_{1/2}$ (h)	25.057 ± 4.9743	25.206 ± 4.8367
AUC_% Extrap_obs (%)	4.409 ± 6.4111	3.730 ± 3.4725

Table 2: Geometric Least Squares Mean, Ratios and 90% Confident Interval for pioglitazone (N=46)

Parameters (Units)	ln-transformed Geometric Least Squares Mean (n=46)			90% Confidence Interval (Parametric)
	Reference Product-A	Test Product-B	Ratio (B/A) %	
C_{max} (ng/mL)	1353.508	1314.636	97.1	87.49-107.82%
AUC_{0-t} (ng.h/mL)	12199.474	11976.272	98.2	90.76-106.18%
$AUC_{0-\infty}$ (ng.h/mL)	12799.684	12448.656	97.3	90.23-104.83%

Table 3: Descriptive Statistics of Formulation Means for M4 metabolite (N=46)

Parameters (Units)	Mean ± SD (Untransformed data)	
	Reference Product-A	Test Product-B
T_{max} (h)	17.391 ± 7.6230	17.783 ± 6.6296
C_{max} (ng/mL)	709.789 ± 176.4613	693.672 ± 169.1421
AUC_{0-t} (ng.h/mL)	41989.556 ± 11114.2926	40787.609 ± 11041.8663
$AUC_{0-\infty}$ (ng.h/mL)	42882.529 ± 11176.6015	42275.797 ± 11217.2335
λ_z (1/h)	0.0275 ± 0.00485	0.0275 ± 0.00465
$t_{1/2}$ (h)	25.956 ± 4.4614	25.943 ± 4.4838
AUC_% Extrap_obs (%)	2.226 ± 1.2532	3.351 ± 6.5240

The ratio of geometric least squares mean of test and reference formulations for In-transformed pharmacokinetic parameter Cmax was 97.1 %. The two one-sided 90% confidence interval for the ratio of geometric least squares mean was found to be 87.49-107.82%. This interval is within the acceptance limits of75-133% required for the conclusion of bioequivalence.

The ratio of geometric least squares mean of test and reference formulations for In-transformed pharmacokinetic parameter AUC o-t, was 98.2%.The two one-sided 90% confidence interval for the ratio of geometric least squares mean was found to be 90.76-106.18%. This interval is within the acceptance limits of 80-125% required for the conclusion of bioequivalence.

The ratio of geometric least squares mean of test and reference formulations for In-transformed pharmacokinetic parameter AUCo~ was 97.3%. The two one-sided 90% confidence interval for the ratio of geometric least squares mean was found to be
90.23-104.83%. This interval is within the acceptance limits of 80-125%, required for the conclusion of bioequivalence.

Safety data

A total of twelve adverse events were reported during the conduct of the trial. All the adverse events were mild in nature and were resolved. No deaths or serious adverse events were reported during the study.

Conclusions

Based on the presented bioequivalence study Pioglitazone Accord 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 Post marketing experience

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

2.4.5 Discussion on Clinical aspects

One bioequivalence study 068-05 was provided for Pioglitazone Accord application. The bioequivalent study and statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). The parameters used to establish bioavailability included the area under the plasma concentration-time curve and the maximal plasma concentration of the parameter compound of pioglitazone. Bioequivalence has been established as the calculated 90% confidence intervals for In-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} fell within the acceptance range of 80-125% for the parent drug pioglitazone as required by the above mentioned guideline.

2.4.6 Conclusions on clinical aspects

The bioequivalence study showed that the 90% confidence intervals of the test/reference (T/R) ratio lie within the prospectively defined acceptance criteria of 80-125% for AUC_{0-t}, AUC_{0-inf} and C_{max}. The applicant has documented bioequivalence between (Actos marketed by Takeda Global Research and Development Centre (Europe) Ltd) and Pioglitazone Accord and therefore, a similar safety and efficacy profile to the reference pioglitazone Actos can be assumed.

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 on 27 October 2010. 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 cycle

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 August 2011 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 as described below. 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 a cross-over design under fasting conditions. 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 times 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 Accord met the protocol-defined criteria for bioequivalence when compared with the reference product, Actos. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} 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 Accord 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;

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.

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

Pioglitazone Accord (EMEA/H/C/2277)

Divergent statement

We have a divergent opinion on the above mentioned 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: ……