London, 19 January 2012
EMA/210151/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pioglitazone Actavis

International nonproprietary name: pioglitazone

Procedure No. EMEA/H/C/002324

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

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Product information

Marketing authorisation application

Name of the medicinal product:	Pioglitazone Actavis
Applicant:	Actavis Group PTC ehf Reykjavíkurvegur 76 - 78 IS-220 Hafnarfjörður Iceland
Active substance(s):	pioglitazone hydrochloride
International Nonproprietary Name/Common name:	pioglitazone
Pharmaco-therapeutic group (ATC Code):	Thiazolidinediones (A10BG03)
Therapeutic indication(s):	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. 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 (see section 4.4).
Pharmaceutical form(s):	Tablet
Strength(s):	15 mg, 30 mg, 45 mg
Route(s) of administration:	Oral use
Packaging:	blister (alu/alu)
Package size(s):	14, 28, 30, 50, 56, 84, 90, 98 and 100 tablets

Reference medicinal product (used in bioequivalence study)

Name of the medicinal product:	Actos
Marketing Authorisation Holder	Takeda Global Research and Development Centre (Europe) Ltd.
Active substance(s):	pioglitazone hydrochloride
International Nonproprietary Name/Common name:	pioglitazone
Therapeutic indication(s):	Pioglitazone is indicated as second or third line treatment of type 2 diabetes mellitus as described below: o as monotherapy - in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance o 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. o 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. 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 (see section 4.4).
Pharmaceutical form(s):	Tablets
Strength(s):	15 mg, 30 mg, 45 mg
Route(s) of administration:	Oral use

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List of Abbreviations

Alu	Aluminium
ANOVA	Analysis of variance
ASMF	Active Substance Master File
AUC0-t	area under the plasma concentration versus time curve from time zero to the last measurable concentration
AUC0-∞	area under the plasma concentration versus time curve extrapolated to infinityClast
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum measured plasma concentration
CPMP	Committee for Proprietary Medicinal Products
CV%	percentage coefficient of variation
DSC	Differential Scanning Calorimetry
EC	European Commission
EDTA	Ethylenediaminetetraacetic acid
EMA or EMEA	European medicines agency
EU	European Union
GCP	Good Clinical Practice (GCP)
GMP	Good Manufacturing Practice (GMP)
HbA1C	Haemoglobin A1C
HPLC	High Performance Liquid Chromatography
ICH	International Conference on harmonisation
INN	International Nonproprietary Name
IR	Infrared spectroscopy
Kel	Elimination rate constant
LSM	Least Square Means
MA	Marketing Authorisation
MAH	Marketing authorisation holder
MW	Molecular Weight
NMR	Nuclear Magnetic Resonance
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMP	risk management plan
SmPC	Summary of product characteristics
t1/2 -	elimination or terminal half-life

Tmax	time of maximum measured plasma concentration
T/R ratio	Test product /Reference product ratio
XRD	X-ray diffraction

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 29 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pioglitazone Actavis, 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 22 April 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.

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 (see section 4.4)."

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 mg, 30mg Tablets

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 number: 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 mg, 30mg, 45 mg Tablets
- 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 number: EU/1/00/150/001-030

- 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 30 mg and 45 mg Tablets
- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd.
- Date of authorisation: 30 mg: 13 October 2000, 45 mg: 16 September 2003
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/00/150/011-015, 022-024, 029-030 and EU/1/00/150/004-006, 008, 010, 019-021, 027
- Bioavailability study number(s): 2205/10 and 994/06

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 was Patrick Salmon.

- The application was received by the EMA on 29 October 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 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 20 April 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 July 2011.
- During the CHMP meeting on 18 – 21 July 2011, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant. The final List of Outstanding Issues was sent to the applicant on 21 July 2011.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 August 2011.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 September 2011 and updated on 16 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 Actavis.
- 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 Actavis.

2 Scientific discussion

2.1 Introduction

Pioglitazone Actavis is a generic medicinal product containing pioglitazone (as pioglitazone hydrochloride) as active substance.

The reference medicinal product is Actos 15, 30, 45 mg tablet. In addition to the presentations authorised for Actos, the applicant has added the 100 pack size. The proposed pack sizes are consistent with the dosage regimen and duration of use.

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.

The indication for Pioglitazone Actavis is different from the reference medicinal product Actos due to patent reasons. The indication of the reference medicinal product Actos is:

"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.

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 indication of Pioglitazone Actavis is:

"Pioglitazone is indicated as second or third line treatment of adult patients with 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.

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.

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

Pioglitazone Actavis is presented as tablets containing pioglitazone hydrochloride as active substance. Three strengths have been developed: 15, 30 and 45 mg. All strengths have the same proportional composition and bear sufficient features to differentiate. For a full list of excipients refer to the SmPC. The tablets are packaged into Alu/Alu blisters.

2.2.2 Active Substance

Pioglitazone (INN) is an established active substance of chemical origin. Its chemical name is (±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride. The molecular formula is $C_{19}H_{20}N_2O_3S.HCl$, and molecular mass 392.90. The chemical structure of the molecule has been established by spectral (UV, IR, 1H and 13C NMR and mass spectra) elemental and thermal (DSC) analyses.

Currently pioglitazone hydrochloride is not described in the European Pharmacopoeia or pharmacopoeia of a Member State. However, a draft monograph has been published in PharmEuropa Vol. 22, No. 4.

Full information about the active substance has been provided by the active substance supplier and the finished product manufacturer in the Module 3. Acceptable QP declarations confirming the active substance is manufactured in compliance with GMP have been provided in annex 5.22 of Module 1.

Pioglitazone hydrochloride appears as a white to off-white crystalline powder which is practically insoluble in water. Solubility is highly pH dependent. It exhibits stereoisomerism and the active substance is a racemic compound. It exists at least in two different crystal forms, referred to as polymorph I and polymorph II. Batch analysis data confirm that polymorph I is routinely produced by the synthetic process defined by both active substance suppliers, and it is used in the manufacture of the finished product.

Manufacture

At the time of the CHMP opinion pioglitazone hydrochloride is supplied by two manufacturers. Both manufacturers have provided an Active Substance Master File (ASMF). The active substance is synthesised in several steps using commercially available starting materials. The process is adequately described and satisfactory specifications have been set for the starting materials, reagents and solvents used in the process. All critical in-process controls parameters are well established and justified. All relevant impurities (including potentially genotoxic impurities), degradation products and residual solvents have been investigated and appropriately characterised. A number of genotoxic impurities have been identified and data have been provided to confirm that they are either not present in the active substance or they are appropriately controlled in an intermediate or the active substance itself. A justification of the limits applied has been provided.

Specification

The active substance specification is generally adequate to control the quality of the active substance. It includes tests and limits for appearance, assay (HPLC), identification (pioglitazone: IR, HPLC), identification of chlorides (Ph. Eur.), solubility (Ph. Eur.), related substances including potentially

genotoxic impurities (HPLC), residual solvents (GC), residual reagents (Ph. Eur.), water content (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), ionic chloride (potentiometric titration), optical rotation, benzene, polymorphism (Ph. Eur., XRD) and particle size distribution (laser diffraction).

All active substance specifications are considered adequately justified and the non-compendial analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines.

Batch analysis data from three consecutive production scale batches from each active substance manufacturer have been provided. The results confirm batch-to-batch consistency and compliance with the proposed specifications.

Stability

Data from stability studies on three production scale batches from each active substance manufacturer have been provided. Samples were stored for up to 48 months under long term conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH) in accordance with ICH requirements. All batches have been tested for conformance with the specifications using stability indicating analytical methods. The specifications tested were description, identification (IR), polymorphism (XRD), water content, related substance and assay (HPLC). In all cases the batch analysis data met the predefined specifications and no significant changes were observed.

In addition stability data have been provided under stress conditions (heat, acid hydrolysis, base hydrolysis, photo degradation, water hydrolysis and hydrogen peroxide treatment).

The stability data provided by both active substance manufacturers support the proposed re-test periods at the proposed packaging and storage conditions.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The aim of the initial development was to formulate a tablet similar to the reference product. Flow properties of the active and excipients, were considered for the selection of a suitable manufacturing method. The effect of binder concentration, water content and resistance to crushing were investigated and the final formulation was chosen.

Pioglitazone hydrochloride is practically insoluble in water. It is classified as a class II (low solubility, high permeability) drug in the biopharmaceutics classification system. As a result of the low solubility a specification for particle size was set by the drug product manufacturer. Both suppliers have confirmed that they consistently manufacture the same polymorphic form. It has further been demonstrated that no change in the polymorphic form occurs during manufacture and storage.

The choice of excipients was based on the qualitative composition of the reference product. The excipients used are well known and widely used within the pharmaceutical industry. Compatibility of the active substance with the excipients has been demonstrated on stability.

In-vitro dissolution comparisons between the test and reference products have been provided. The reference product was sourced from the UK market. The test and reference products were observed to behave similarly for all strengths tested in all media. In media at pH 1.2 >85% was released in 15 minutes for test and reference at all strengths. At pH 4.5 and 6.8 release is much slower and

incomplete. The reduced dissolution at pH 4.5 and pH 6.8 is expected as pioglitazone hydrochloride is known to be insoluble at these pHs.

Similarity factors have not been provided in line with the Guideline on the investigation on bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), however it can be concluded that, given the known insolubility of the active at the pH 4.5 and 6.8 and the similarity of the dissolution profiles of the test and reference products those pH's it is evident that the reduction in solubility observed at pH 4.5 and 6.8 is as a result of the intrinsic solubility issues with the active substance and is not related to the formulation and no further information is requested in relation to the proposed biowaiver from the quality point of view.

Only one bioequivalence study was performed on the 30mg strength. During the procedure, data on a second bioequivalence study with 45 mg tablets were provided; for further details see the clinical section of the AR. It is agreed that that bioequivalence studies are not required on the other strength since all of the conditions listed in section 4.6.1 of Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) are considered fulfilled. Refer also to the clinical AR for discussion on the acceptability of the biowaiver.

The impurity profiles of the 15mg, 30mg and 45mg test tablets were also compared with one batch of Actos 30mg tablets. All results complied with the proposed release specification limits.

The manufacturing process is a conventional wet granulation process.

Adventitious agents

Lactose monohydrate is the only excipient that is derived from animals. As pr the supplier statement it complies with the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy (EMEA/410/rev 2).

Manufacture of the product

The manufacturing process is simple and consists of five steps. The information provided on in-process controls and process validation is acceptable. The proposed holding times have been defined and data have been provided to support them.
Process validation has been successfully carried out on six pilot scale batches manufactured by the proposed manufacturer on two batches for each strength using active substance from one of the proposed suppliers. Results show the product can be consistently manufactured.
A process validation scheme for the production scale batches has been provided and agreed.

Product Specification

The drug product release and shelf life specifications include tests and limits for appearance (visual), identification (HPLC-DAD), friability (Ph. Eur.), resistance to crushing (Ph. Eur.), Uniformity of dosage units (Ph. Eur.- mass variation), average tablet mass (weighing), dissolution (UV, Ph. Eur.), rekated substances (HPLC), assay (HPLC) and microbiological quality (Ph. Eur.).
Batch analysis data have been provided on four pilot scale batches of each strength. The active substance used in these batches was supplied by both suppliers. All of the results comply with the release specifications. Certificates of analysis for these batches have also been provided.

Stability of the product

Stability studies were undertaken on two pilot scale batches of each strength manufactured using active substance from one of the suppliers stored at 25±2°C/60±5% RH for up to 36 months and at 40±2°C/75±5% RH for six months. Results from two smaller scale batches for the 15mg and 45mg strengths one of each strength using active substance manufactured by the second supplier were also provided as supportive data. All batches were manufactured at the proposed manufacturing site and the container closure system was as that to be marketed. The testing conditions and intervals were according to ICH Q1A (R2).

In addition, two pilot scale batches from each strength using active substance manufactured from the second supplier (including the second biobatch) have been placed on stability. Only 3 months data have become available, but are in line with previous batches.

All results at both 25°C/60% RH and 40°C/75% RH are within specification and no trends were observed. The results do however comply with the specifications and are acceptable for product manufactured with active substance from both manufacturers.

On the basis of the stability results provided the proposed shelf life and storage conditions are acceptable.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has 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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

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 March 2009 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 bioequivalence study with cross-over design under fasting conditions comparing 30 mg tablets. Since this dose was not fully justified, the applicant, during the procedure, provided data of a second bioequivalence study with 45 mg tablets as additional evidence to support the first study.

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

If the generic medicinal product has the same manufacturer, same qualitative composition, same ratio between active substance and excipients, comparable in vitro dissolution profile as the reference product, these aspects could be used to justify an exemption from the requirement to perform bioequivalence studies. However, for the (first) bioequivalence study, the applicant chose the dose of 30 mg and no clear justification was provided. The relevant guidance on Investigation of Bioequivalence states that with product with linear pharmacokinetics, the study should in general be conducted at the highest strength. To address the issue of testing with the highest dose the applicant therefore commissioned a new study using 45 mg as the dose.

Clinical studies

A bioequivalence study with 30 mg tablets has been submitted initially and a second study with 45 mg tablets has been submitted during the procedure.

2.4.2 Pharmacokinetics

Methods

Study design

The initially submitted study was a randomised, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Pioglitazone 30 mg tablets of Actavis Group hf, Iceland and Actos (Pioglitazone) 30 mg tablets of Takeda Europe R & D Centre Limited, London, UK, in healthy adult subjects of either sex, under fasting conditions.

The study was performed at Lotus Labs Pvt, Mylapore, Chennai, India, in 2006.

After an overnight fast (i.e. at least 10 hours of fasting), subjects were given the test or the reference product with 240 ml of water. Water was not permitted 1 hour before dosing and until 2 hours post-dosing. The subjects were served a first meal (lunch) at t=4 h. in both periods.

Blood samples were collected at t= 0h and 0.5, 1, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose.

There was a washout period of 14 days between dosing

Test and reference products

The test product was Pioglitazone 30 mg tablets (Actavis Ltd., Malta); Batch No.: S09390. The reference product was Actos 30 mg tablets (Takeda Ireland Ltd.); Batch No.: 9230021A.

Population(s) studied

Thirty eight adults subjects of either sex and 33 completed the study.

Healthy adult subjects of either sex between 18-55 years of age (inclusive), with a body mass index (BMI) between 18.5 and 24.9 kg/m2; subjects who have no evidence of underlying disease during screening medical history and physical examination and screening laboratory values.

5 subjects dropped out of the study: The reasons for the drop out were for 3 subject withdrawal of their consent; for 1 subject non-compliance, and for 1 subject a lower respiratory infection.

Analytical methods

The plasma product concentrations were determined using a validated high performance liquid chromatographic method for the determination of pioglitazone, hydroxy pioglitazone and keto pioglitazone in human EDTA K3 plasma over the range 10.06 to 2012.80 ng/ml for pioglitazone, 10.08 to 1008.20 ng/ml for hydroxypioglitazone and 2.00 to 400.00 ng/ml for ketopioglitazone.

Pharmacokinetic Variables

The following parameters were calculated:

1. AUC_{0-t} using the linear trapezoidal rule
2. $AUC_{0-\infty}$ by adding the quantity C_{last}/K_{el} to AUC_{0-t}.
3. C_{max}

Statistical methods

The following summary statistics for the pharmacokinetic parameters were calculated for both the test product (A) and reference product (B): number of subjects, arithmetic mean (mean), standard deviation (S.D.), minimum, maximum, median and percentage coefficient of variation (CV%). Additionally, geometric means (GM) were estimated for AUC0-t, AUC0-∞ and Cmax.

The log-transformed pharmacokinetic parameters (AUC0-t, AUC0-∞ and Cmax) were analyzed using the ANOVA model. The ratio of the Test and Reference product averages (Least Square Means) was estimated for the differences in the Least Square Means (LSM) of the log-transformed data then taking the anti-log of the estimates. The 90% Confidence Interval for the ratio of the Test and Reference was estimated using the difference of least square mean between test and reference (estimate), the 't' value at Mean Square Error Degrees of Freedom (df) and the Standard Error of Estimate. The Standard Error of Estimate was calculated using the Mean Square Error and the number of reference subjects from the GLM - ANOVA Model. The number of subjects to be included was calculated to be 34

if the difference between test and reference is 5%. Taking into account possible dropouts, 38 subjects were considered for this study. The statistical considerations were considered as adequate by CHMP.

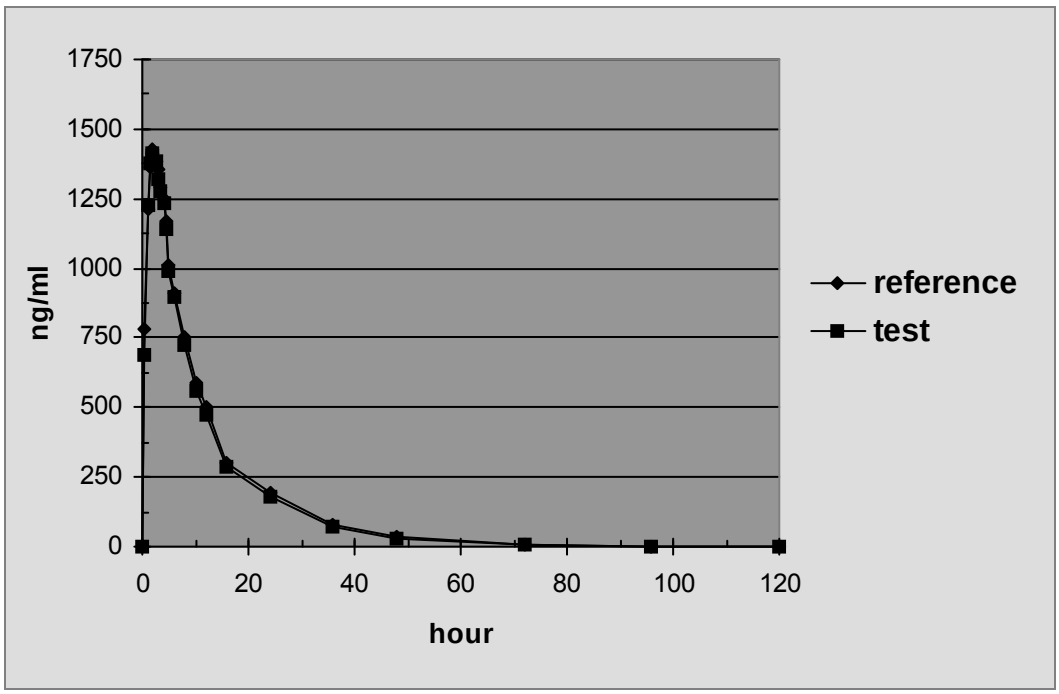
The overall conduct of the bioequivalence study was acceptable. Patients were fasted overnight and received a single oral dose of 1 tablet containing 30mg of pioglitazone, with 240 mL of water.

Results

Table 1: Summary Statistics of Pharmacokinetic Parameters for Pioglitazone 30 mg Tablets in Healthy Adult Subjects

Parameters	Statistics	Test	Reference
AUC_{0-t} (ng.h/ml)	Arithmetic Mean	16208.252	16931.202
	S.D.	3205.886	5436.627
	C.V. (%)	19.78	32.11
	Median	16287.929	16945.559
	Minimum	7816.478	6405.503
	Maximum	23350.041	34318.218
	Geometric Mean	15877.420	16092.041
	No of Subjects	33	33
$AUC_{0-\infty}$ (ng.h/ml)	Arithmetic Mean	16609.465	17374.729
	S.D.	3287.735	5451.504
	C.V. (%)	19.79	31.38
	Median	16573.223	17102.037
	Minimum	8341.026	6597.284
	Maximum	23479.900	34668.717
	Geometric Mean	16273.566	16550.025
	No of Subjects	33	33
C_{max} (ng/ml)	Arithmetic Mean	1525.521	1546.988
	S.D.	336.902	460.121
	C.V. (%)	22.08	29.74
	Median	1600.610	1561.710
	Minimum	817.320	586.330
	Maximum	2038.860	2545.860
	Geometric Mean	1484.052	1472.362
	No of Subjects	33	33
T_{max} (h)	Arithmetic Mean	1.95	1.78
	S.D.	0.72	0.75
	C.V. (%)	36.66	42.24
	Median	1.75	1.75
	Minimum	1.00	0.50
	Maximum	4.00	3.50
	No of Subjects	33	33

Fig.1: pioglitazone plasma concentrations after reference and test with 30 mg tablets.



This study suggests that the requirements for claiming bioequivalence of the described test-formulation are fulfilled: for all key pharmacokinetic parameters listed in the relevant guidelines, the 90% CI of all ratio's are within the 80% - 125% range.

Safety data

A total of 12 adverse events were reported during the course of the study. Two AEs were related to study products and were mild to moderate in intensity. Ten AEs were unrelated to study products out of which 05 were moderate and 05 mild in intensity. All the adverse events resolved completely without any sequelae. 1 subject experienced sweating with the test product and one subject experienced symptoms of hypoglycaemia also with the test product (moderate and resolved). There were no reports of hypoglycaemia with the reference. Glucose solution was administered to both subjects as 60ml 20% glucose. The CHMP did furhter question these cases and it was clarified by the applicant that there was no documented hypoglycaemic event and patients were treated rather on symptoms of hypoglycaemia.

Second bioequivalence study with 45 mg tablets

Brief summary of the bioequivalence study with data with 45 mg tablets.

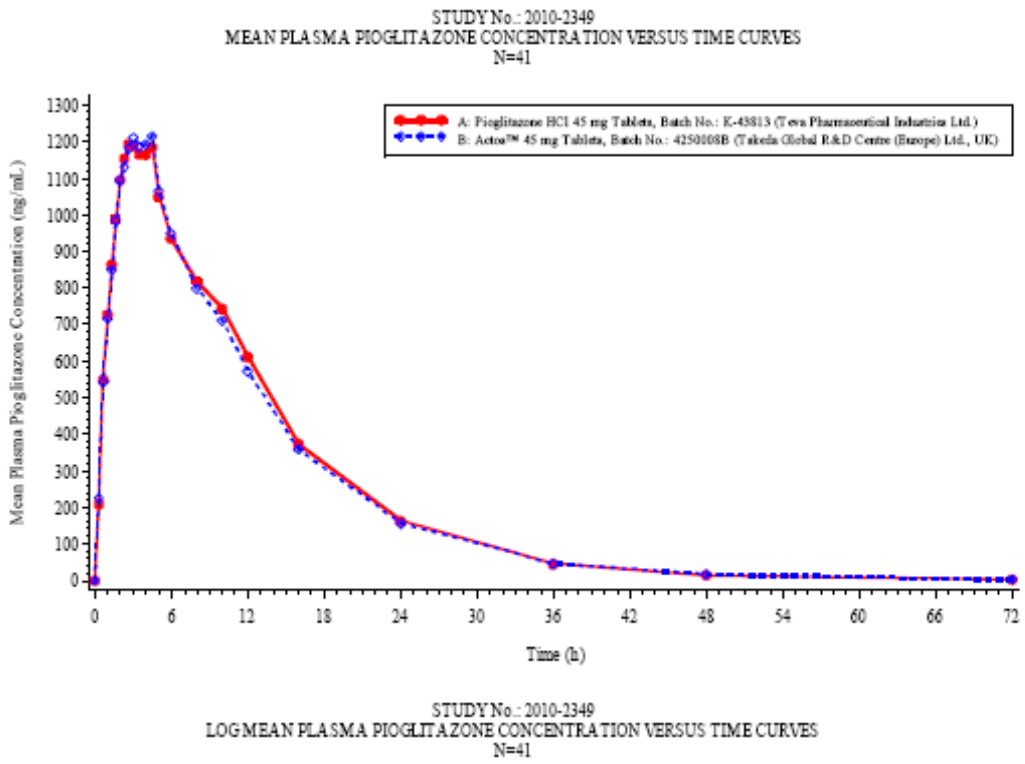
Table 2: Synopsis:

objective of the study	to assess the bioequivalence of pioglitazone 45 mg tablets from Actavis Group PTC ehf, Iceland and Actos® 45 mg tablets of Takeda Global Research and Development Centre (Europe) Ltd, UK in healthy adult subjects and under fasting conditions.
study design	this bioequivalence study was a classical two treatment, two sequences, two period, cross-over study. 38 healthy adult male subjects were enrolled of which 2 dropped out. All subjects were housed from at least 11 hours before dosing until after 48 hours post dose blood draw in both periods. Subjects were dosed with the test or the reference product in each period as determined by the randomization schedule. Treatments were separated by a washout period of 7 days.
sampling scheme	samples were collected at t= 0 h and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.333, 2.667, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 h post dose in both periods
sample size N	38 healthy adult male subjects were included: 36 completed both periods. These were included in the PK and statistical analyses of this review
subjects	healthy male subjects; all non-smokers
test formulation	pioglitazone 45 mg tablets (batch no: F26042 (S54040))
manufacturing date	06-09-2010
batch size	110000 tablets
reference formulation	Actos® 45 mg tablets (batch no: 4250025B)
exp date	October 2012
route of administration	oral
manufacturer of test	Actavis Ltd BLB016 Bulebel; Ind.Estate, Zejtun, ZTN 3000 Malta
Marketing authorization holder	Takeda Global Research & Development Centre (Europe) Ltd; Arundel Great Court; 2 Arundel Street; London UK
CRO	Lotus Labs Pvt. Ltd.;No. 02, M.M Towers; Jakkur Plantations; Yelahanka Hobli; Bangalore - 560 064
site of study	study was conducted at the CRO site
GLP/GCP compliance	This study was conducted in compliance with Good Clinical

Table 3: Estimate of test/reference AUC0-t, AUC0-∞-ratio with the 90% CI for pioglitazone

	point estimate	*lower end*	*upper end*
C_{max}	99.546	88.575	111.875
AUC_{0-t}	96.284	89.056	104.099

Figure 2: Mean pioglitazone plasma concentrations for Pioglitazone Actavis and Actos:



Conclusions

Based on the presented two bioequivalence studies Pioglitazone Actavis 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

Two open-label, single-dose, randomized, crossover bioequivalence studies were carried out to compare 30 mg tablets and 45 mg tablets, respectively. Overall, the design of the trial and the analytical methods used were adequate. Protocol violations were considered to be minor. The ratios and the corresponding 90% confidence intervals (test versus reference) for AUCt, AUC∞ and Cmax were successfully used to demonstrate bioequivalence.

2.4.7 Conclusions on clinical aspects

Bioequivalence between Pioglitazone Actavis and Actos has been demonstrated as the 90% confidence intervals for the ratios of the test to reference product were found to lie within the pre-specified range both for the 30 mg tablets and the 45 mg tablets.

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 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 February 2012 as its data lock point.

2.6 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:
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.

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 indication for Pioglitazone Actavis is different from the reference medicinal product Actos due to patent reasons.

The indication of Pioglitazone Actavis is:
"Pioglitazone is indicated as second or third line treatment of adult patients with 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.

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.

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."

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 studies form 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 methods were validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pioglitazone Actavis met the protocol-defined criteria for bioequivalence when compared with Actos. The results of the two bioequivalence studies suggested that the requirements for claiming bioequivalence of the described test-formulation are fulfilled: for all key pharmacokinetic parameters listed in the relevant guidelines, the 90% CI of all ratio's are within the 80% - 125% range.

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 decision that the benefit-risk balance of Pioglitazone Actavis in the indication below:

"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.

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 (see section 4.4)."

is favourable and 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

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

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.

PSUR cycle

The PSUR submission schedule should follow the PSUR submission schedule for 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 risk 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 Actavis (EMEA/H/C/002324)

Divergent statement

We have a divergent position from the above mentioned positive opinion recommending granting of Marketing Authorisations 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: ……