EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

Pioglitazone ratiopharm

International non proprietary name: pioglitazone

Procedure No. EMEA/H/C/0002260

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

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List of Abbreviations

Alu	Aluminium
ASMF	active substance master file
BE	Bio-equivalence
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
DSC	
EMA or EMEA	European Medicines Agency
EC	European Commission
EU	European Union
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
ICH	International Conference on harmonisation
INN	International Nonproprietary Name
IR	Infrared
LDPE	Low Density Polyethylene
LDPP	Low Density Polypropylene
MS	Mass spectrometry
NF	National Formularium
NMR	Nuclear Magnetic Resonance
GMP	Good Manufacturing Practice (GMP).
Ph.Eur.	European Pharmacopoeia
Rev.	Revision
SmPC	Summary of Product TSE
USP	Unites States Pharmacopoeia
UV	Ultraviolet
XRD	X-ray diffraction

1 Background information on the procedure

1.1 Submission of the dossier

The applicant ratiopharm GmbH submitted on 27 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pioglitazone ratiopharm, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised medicinal product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP during its meeting on 14-17 December 2009.

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 in the treatment of type 2 diabetes mellitus:

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 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, 30 mg tablets**
- Marketing authorisation holder: **Takeda Global Research and Development Centre (Europe) Ltd, UK**
- Date of authorisation: **13-10-2000**
- Marketing authorisation granted by: Community
  - Community Marketing authorisation number: **15 mg: EU/1/00/150/001-003, 007, 009, 016-018 & 30 mg: EU/1/00/150/004-006, 008, 010, 019-021**

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

- Product name, strength, pharmaceutical form: **Actos 15 mg, 30 mg, 45 mg tablets**
- Marketing authorisation holder: **Takeda Global Research and Development Centre (Europe) Ltd, UK**
- Date of authorisation: **13-10-2000**
- Marketing authorisation granted by: Community
  - Community Marketing authorisation number:
    15 mg: EU/1/00/150/001-003, 007, 009, 016-018
    30 mg: EU/1/00/150/004-006, 008, 010, 019-021
    45 mg: EU/1/00/150/011-015, 022-024

■ 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, UK**
- Date of authorisation: **16-09-2003**
- Marketing authorisation granted by: Community
  - Community Marketing authorisation numbers: **EU/1/00/150/011-015, 022-024**
- Bioavailability study numbers: **PON-P7-060 and 90236**

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:

Rapporteur: Patrick Salmon

- The application was received by the EMA on 27 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 to 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 18 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 April 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2011.
- During the CHMP meeting on 20 to 23 June 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 applicant submitted the responses to the CHMP consolidated list of outstanding issues on 01 July 2011.
- During the meeting on 18 to 21 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pioglitazone ratiopharm on 21 July 2011.

2 Scientific discussion

2.1 Introduction

Pioglitazone ratiopharm is a generic medicinal product containing pioglitazone as active substance. Three strengths have been developed; 15 mg, 30 mg and 45 mg tablets. The reference medicinal product Actos has been centrally authorized on 13 October 2000 and is also available as 15 mg, 30 mg and 45 mg tablets. Together with the opinion on this medicinal product, the CHMP adopted a positive opinion for two multiple applications submitted by ratiopharm GmbH. The three pioglitazone generics (Pioglitazone ratiopharm, Pioglitazone ratiopharm GmbH and Pioglitazone ratio) slightly differ in indication due to patent reasons.

Pioglitazone is a thiazolidinedione compound that acts as a peroxisome proliferator activating receptor (PPAR)-γ agonist with potential benefits on insulin resistance. Pioglitazone 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 approved indication for Pioglitazone ratiopharm is identical to the current indication of the reference medicinal product Actos:

"Pioglitazone is indicated in the treatment of type 2 diabetes mellitus:
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 therapy with pioglitazone may be initiated at 15 mg or 30 mg once daily. The dose may be increased in increments up to 45 mg once daily. In combination with insulin, the current insulin dose can be continued upon initiation of pioglitazone therapy. If patients report hypoglycaemia, the dose of insulin should be decreased. Pioglitazone tablets are taken orally once daily with or without food. Tablets should be swallowed with a glass of water.

The applicant has developed pioglitazone tablets of 15 mg, 30 mg and 45 mg strength and has shown bioequivalence with the reference medicinal product Actos. All the clinical and non-clinical experience on Actos is therefore relevant for Pioglitazone ratiopharm tablets. According to the legislation the applicant is not required to provide the results of pre-clinical tests and clinical trials if it is demonstrated that the proposed medicinal product is a generic of a reference medicinal product which is authorised for 6/10 years in a Member State or in the Community.

Pioglitazone ratiopharm is presented in thirteen pack sizes for each strength; blisters of 14, 20, 28, 30, 50, 56, 60, 84, 90, 98 or 100 tablets and bottles containing 100 or 500 tablets. At the time of the CHMP opinion, the 20, 60, 100 and 500 tablets pack size does not exist for the reference product. The highest pack size of the reference product contains 196 tablets. Nevertheless, the proposed pack sizes are consistent with the dosage regimen and duration of use.

The applicant did not apply for a combined printed package leaflet for the different tablet strengths.

2.2 Quality aspects

2.2.1 Introduction

Pioglitazone ratiopharm is presented as tablets containing the active substance pioglitazone (as hydrochloride). Three strengths have been developed: 15 mg, 30 mg and 45 mg. Other ingredients are defined in the SmPC, section 6.1. The appearance is the same for all strengths: white, flat round tablets with no marking and no score line, but have a different diameter according to the strength. The tablets are packed in aluminium/aluminium blisters or in high density polyethylene (HDPE) bottles-white LDPP cap.

2.2.2 Active Substance

This medicinal product contains as active substance pioglitazone hydrochloride. The International Nonproprietary Name (INN) is pioglitazone. 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 $C_{19}H_{20}N_2O_3S.HCl$, Mol.Wt. 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. Pioglitazone hydrochloride exhibits stereoisomerism due to the presence of one chiral center and is synthesized and used as a 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 defined 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 ratiopharm 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

Pioglitazone is not described in the European Pharmacopoeia or a pharmacopoeia of a Member State. However, a draft monograph has been published in PharmEuropa 22.4 and an official monograph for both the active substance and the finished dosage form (tablets) is published in the USP 34-NF 29 and has entered into force on 1st May 2011.

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), particle size distribution (laser diffraction), residual solvents (GC), dimethyl formamide and methyl acrylate content (GC) and nickel content (AAS). In addition to these, the applicant's specifications include tests for identification (by HPLC), melting point, polymorphism, sulphated ash and thiourea. The specifications and tests proposed by the active substance manufacturer and applicant 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. Certificates of analysis have been provided for the active substance tested against the applicant's active substance specifications. 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. (monograph 3.1.3) 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 applicant's objective was to develop a generic equivalent to the European reference product Actos that is available as immediate release tablets containing 15 mg, 30 mg or 45 mg pioglitazone hydrochloride. The aim was to develop generic immediate release tablets which are bioequivalent with the reference product and demonstrate to have a satisfactory disintegration time, content uniformity and dissolution profile.

Pioglitazone ratiopharm tablets contain the same excipients as the reference medicinal product Actos, hence compatibility with the active substance is considered established. All excipients comply with the Ph.Eur. and are commonly used in this type of formulation.

During the development, the applicant considered the key active substance properties that can influence the quality of the medicinal product such as the low water solubility, pH, polymorphism (Form I is used), isomerism (racemic mixture) and particle size. Dissolution studies on the finished product demonstrated that the particle size distribution of the final blend needs to be controlled during the manufacturing process of the tablets.

Dissolution studies have been performed at pH 1.2, pH 2.0, pH 4.5 and pH 6.8. The dissolution was rapid at pH 1.2, but due to solubility problems of the active substance, the dissolution was much slower and incomplete at both pH 4.5 and pH 6.8. Given the known insolubility of the active substance at the pH 4.5 and 6.8 and the similarity of the dissolution profiles of the test and reference product at 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. The *in vitro* dissolution studies demonstrated that the Pioglitazone ratiopharm tablets and the Actos tablets have equivalent release of the active substance.

Pioglitazone ratiopharm tablets were developed in three different strengths, i.e. 15 mg, 30 mg and 45 mg. The bioequivalence study was performed with the 45 mg tablet. The applicant fulfilled the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) and extrapolated the results of the bioequivalence study performed on the 45 mg strength to two lower strengths; 15 mg and 30 mg. Appropriate *in vitro* dissolution data confirmed the adequacy of waiving additional *in vivo* bioequivalence testing.

Adventitious agents

A TSE declaration was submitted to confirm that magnesium stearate is of vegetable origin. Lactose monohydrate is derived from milk and is therefore compliant with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 2). No excipients derived from human origin have been used.

Manufacture of the product

Pioglitazone ratiopharm tablets are manufactured by using conventional granulation followed by sieving, drying, sieving, blending and compression. The manufacturing process is considered standard for immediate release tablets. Adequate in-process controls are performed. The acceptance criteria and the test methods are adequately chosen to ensure that the drug product will comply with the specification limits. A detailed manufacturing description and flow scheme have been provided.

The applicant has presented a validation plan outlining the process validation strategy on commercial scale batches. The validation study will be carried out on all strengths covering the minimum and maximum proposed batch sizes. The proposed sampling plan, tests, acceptance criteria and methodology are considered adequate to validate the manufacturing process of this standard manufacturing process. In addition to the validation plan the applicant has also submitted validation of the manufacturing process for some pilot scale batches. The results obtained indicate that the manufacturing process for the pioglitazone tablets is capable of consistently producing tablets that meet the quality and release specifications as detailed in the finished product specifications.

Product Specification

The finished product release and shelf-life specifications include tests for description (visual), identification of active substance (HPLC, UV), assay (HPLC), content uniformity, related substances and degradation products (HPLC), dissolution, microbiological examination and uniformity of mass of single dose preparations. The finished product specifications are standard for immediate release tablets. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis data provided are produced with active substance from the proposed supplier. The batches were manufactured according to the proposed manufacturing process and packed in proposed packaging material. Batch analysis results comply with the predefined specifications and confirm consistency & uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies have been carried out under long term (25±2°C/60±5%RH), intermediate (30±2°C/65±5%RH) and accelerated (40±2°C/75±5%RH) conditions, on seven pilot scale batches (3 batches for 15 mg and 45 mg strength and 1 batch for 30 mg strength), according to the ICH requirements. Up to 36 months long term and up to 6 months accelerated stability data have been provided. Results for intermediate term conditions (30°C/65% RH) have not been submitted because no significant changes were seen in the results of the accelerated conditions. The parameters tested and analytical methods used are identical to those used for the release specifications, except from content uniformity and uniformity of mass which were not retested at end of shelf-life. The methods used for assay and related substances were proven as stability indicating. The stability batches have been manufactured at the proposed site of finished product manufacture, according to the proposed process and using the active substance obtained from the proposed active substance manufacturer. Stability tests have been carried out in the packaging proposed for marketing, i.e. HDPE bottles (100 and 500 tablets), blisters and bulk.

The stability results demonstrated that pioglitazone content remained well within the specifications under all conditions and that for the other main parameters (dissolution testing and related substances) no trends/change have been noticed throughout the stability studies. Also the microbial results for the primary stability batches in each pack complied with the specifications.

In addition to the above, a bulk stability study and an "in-use stability" (open cap stability) study on opened HDPE bottles is presented covering 6 months at 25°/60%RH. All parameters tested were well

within the specifications and no trend is noted. Considering excellent stability of the tablets, no in-use shelf life needs to be specified.

As part of the stability commitment, the applicant committed that at least one batch of each strength packaged in both HDPE bottles and blisters will be placed on stability annually.

In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4 Discussion on chemical, and pharmaceutical aspects

The Pioglitazone ratiopharm 15 mg, 30 mg or 45 mg tablets is a generic product for Actos which is, like Actos, presented as immediate release tablets and contains the same excipients.

The quality of the active substance is adequately controlled and all excipients comply with the Ph.Eur. The finished product manufacturing process shows to be capable of consistently producing tablets that meet the finished product specifications and appropriate packaging is used to ensure the product remains stable within the agreed shelf-life.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and medicinal 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.

The quality of this medicinal 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. Data has been presented to give reassurance on TSE safety.

At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

2.2.6 Recommendations for future quality development

Not applicable.

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 ratiopharm 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 two bioequivalence studies with cross-over design under fasting conditions. These studies were the pivotal studies for the assessment.

GCP

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

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

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies to demonstrate bioequivalence between their product and the reference product Actos.

Study 90236 was a randomised, two-way cross over, single oral dose, bioequivalence study of two formulations of pioglitazone hydrochloride tablets 45 mg in healthy subjects under fasting conditions.

Study PON-P7-060 was a randomised, two-way cross over, single oral dose, bioequivalence study of two formulations of pioglitazone hydrochloride tablets 45 mg in healthy subjects under fasting conditions.

The applicant performed the second bioequivalence study to take account of improvements in the manufacturing process.

A request for a waiver of bio-study on the remaining strengths (i.e. 15 mg and 30 mg tablets) was submitted and accepted.

2.4.2 Pharmacokinetics

Study 90236

Methods

Study design

Study code: 90236

Title of the study: Randomised, open-label, 2-way crossover, bioequivalence study of pioglitazone 45 mg tablet and Actos (reference) following a 45 mg single-dose in healthy subjects under fasting conditions.

This was a single centre, randomised, single-dose, open-label, 2-way crossover bioequivalence study to compare the rate and extend of absorption of a test pioglitazone versus Actos, a reference pioglitazone, under fasting conditions.

Test and reference products

Treatment Identification:	Test (A)	Reference (B)
Product Name:	pioglitazone (as hydrochloride)	pioglitazone (as hydrochloride) (Actos™)
Company Responsible for Manufacturing:	ratiopharm inc., Canada for ratiopharm GmbH, Germany	Takeda Ireland Limited, Ireland for Takeda Global Research and Development Centre (Europe) Ltd, UK; marketed in Germany
Batch/Lot Number:	2026Z-19	3250059C
Manufacturing Date:	2009.04.29	Not available
Expiration Date:	2009.11.29	07/2011
Strength:	45 mg	45 mg
Dosage Form:	tablet	tablet
Dose Administered:	1 x 45 mg	1 x 45 mg
Route of Administration:	oral	oral

Population(s) studied

Sixty (60) healthy female (N=41) and male (N=19) subjects, aged between 18 and 55 years (inclusion criteria), entered the study. All subjects completed all treatment phases, and analytical results from these 60 subjects were available for statistical analysis.

Analytical methods

The experimental samples were assayed for pioglitazone and its active metabolite hydroxy-pioglitazone using high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS). The required internal standards were pioglitazone-d4 and hydroxy-pioglitazone-d4. The validated calibration curve range used during sample analysis was from 9.92 to 2,974.80 ng/mL for pioglitazone and 9.90 to 1,485.60 ng/mL for hydroxy-pioglitazone and thus adequate for quantitative measurement of analyte concentrations following a 45 mg pioglitazone hydrochloride oral dose.

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, AUC0-t, AUC0-inf and t ½.

Statistical methods

Phamacokinetics:

For pioglitazone:

1. Parametric ANOVA on Cmax, AUC0-t, AUC0-inf and T ½ and Kel; geometric confidence intervals for Cmax, AUC0-t and AUC0-inf; and non-parametric test (Wilcoxon) for Tmax.
2. Factors in the ANOVA model: sequence, subject within sequence, period and treatment.
3. Ln-transformed parameters: Cmax, AUC0-t and AUC0-inf.

For hydroxypioglitazone:

1. Parametric ANOVA on Cmax and AUC0-72; geometric confidence intervals for AUC0-72 and Cmax; and nonparametric test (Wilcoxon) for Tmax.
2. Factors in the ANOVA model: sequence, subject within sequence, period and treatment.
3. Ln-transformed parameters: Cmax and AUC0-72

Criteria for Bioequivalence for pioglitazone:

1. 90% geometric confidence intervals of the ration (A/B) of least-squares means from the ANOVA of the ln-transformed Cmax, AUC0-t should be within 80% to 125%.

Data from hydroxypioglitazone were reported and presented as supportive data.

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.

Parameters		Test (Pioglitazone (A))			Reference (Actos™ (B))		
		Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t}	(ng·h/mL)	14327.50	4796.61	33.48	13959.43	4513.44	32.33
AUC_{0-inf}	(ng·h/mL)	14970.90	4887.45	32.65	14700.30	4547.06	30.93
C_{max}	(ng/mL)	1479.38	531.71	35.94	1420.26	520.72	36.66
Residual area	(%)	4.48	3.62	80.80	5.33	5.58	104.61
T_{max}	(h)	2.39	1.16	48.46	2.52	1.26	49.95
T_{max}*	(h)	2.33	1.50	-	2.50	2.00	-
K_{el}	(h^{-1})	0.0650	0.0348	53.63	0.0605	0.0310	51.31
$T_{½\ el}$	(h)	13.93	7.08	50.80	15.32	9.70	63.31

* Medians and interquartile ranges are presented.

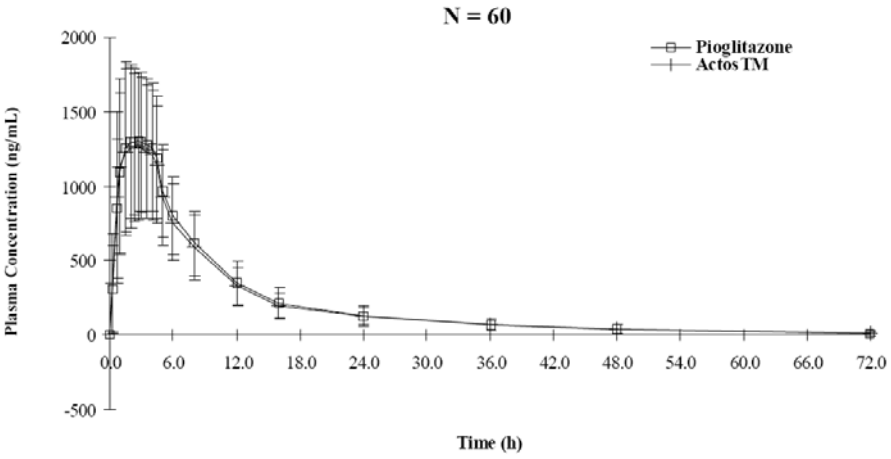
Pioglitazone (A) vs Actos™ (B)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	102.54%	101.51%	105.26%
90 % Geometric C.I.[2]	96.70 % to 108.73 %	96.10 % to 107.22 %	97.16 % to 114.03 %
Intra-Subject CV	19.37 %	18.07 %	26.69 %

The measured mean Cmax and AUC0-t of 1,420 ng/mL and 13,959 ng×h/mL, respectively, for the reference product exceed corresponding data of the published bioequivalence study by 35% and 31%, respectively. This difference can be attributed to the inclusion of 41 female volunteers in the present study as opposed to the published bioequivalence study which was done with males only, because mean Cmax and AUC of pioglitazone are known to be increased in females vs. males by 20% to 60%. The elimination half-lives are comparable in the present and published bioequivalence studies when considering their high variability.

The reference product data for Cmax and AUC are also comparable to the graphed data published by the originator.

Mean plasma pioglitazone concentrations following test and reference product in this study are shown in the Figure below.



Safety data

A total of 42 treatment-emergent adverse events (AEs) were reported by 21 of the 60 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 18 AEs reported by 20.0% (N=12) of the 60 subjects who received Treatment A (test product) and 24 AEs reported by 26.7% (N=16) of the 60 subjects who received Treatment B (reference product). The most common AEs were related to study procedures including "Post-procedural discomfort", "Post-procedural haematoma", "Post-procedural swelling", "Procedural pain", and "Procedural site reaction" and were reported by 20.0% (N=12) of subjects who constituted the safety population. In addition, "Headache" was reported by 15.0% (N=9 [2 subjects after administration of Treatment A, 7 subjects after administration of Treatment B]) of subjects who

constituted the safety population. Though more subjects reported "Headache" following administration of the reference treatment, this AE is a recognised side effect listed in the SmPC.

Of the 42 AEs reported, 28 were graded as mild, 13 were graded as moderate, 1 was graded as severe, and the relationship to study drug of 18 was judged as "possible", 2 as "unlikely", and 22 as "not related". No deaths and serious AEs were reported during this study. One subject experienced the significant AE "Otitis external" and another subject experienced the significant AE "Migraine". The health of these subjects was not at risk during the study. Upon conclusion of the clinical portion of the study, the results from the subjects who completed post-study procedures, including laboratory tests, confirmed the absence of significant changes in the subjects' state of health.

In summary, both formulations were well tolerated, with no serious AEs, and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of AEs.

Study PON-P7-060

Methods

Study design

Study code: PON-P7-060

Title of the study: Single Dose Crossover Comparative Bioavailability of Pioglitazone 45 mg tablets in Healthy Male and Female Volunteers / Fasting state.

This was a single centre, randomised, single-dose, laboratory blinded, 2-period, 2-sequence, crossover bioequivalence study to compare the rate and extend of absorption of a test pioglitazone versus Actos, a reference pioglitazone, under fasting conditions. The study design differs from the other study in that plasma samples were collected beyond 72 h at 96 and 120 h.

Test and reference products

Drug Code:	Test	Reference
Formulation:	Pioglitazone 45 mg tablet	Actos™ 45 mg tablet
Manufacturer:	ratiopharm inc., Canada	Takeda Pharma GmbH, Deutschland
Batch No.:	2026Z-06	1250010A
Manufacturing Date:	2007.05.08	N/AV
Expiry Date:	05/2008	05/2009
Measured Content:	96.1% of label claim	97.6% of label claim

Population(s) studied

Forty-five (45) subjects (16 male and 29 female) of 46 planned subjects were included and completed all treatment phases, and analytical results from these 45 subjects were available for statistical analysis.

Subjects were male or female volunteers, non- or ex-smokers, of at least 18 years of age but not older than 55 years with a body mass index (BMI) greater than or equal to 19 and below 30 kg/m2.

Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (l2-lead ECG), and the usual clinical laboratory tests (haematology, biochemistry, urinalysis) including negative HIV, Hepatitis B and Hepatitis C tests as well as negative screening of ethyl alcohol and drugs of abuse in urine and negative pregnancy test (for female volunteers).

Analytical methods

The experimental samples were assayed for pioglitazone and its active metabolite hydroxy-pioglitazone using HPLC-MS/MS with assay ranges of 9.1 ng/mL to 2,275.3 ng/mL and 4.72 ng/mL to 1,417.36 ng/mL, respectively, and thus adequate for quantitative analysis of analyte concentrations encountered after the 45-mg oral pioglitazone dose.

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, AUC0-t, AUC0-inf and t ½.

Statistical methods

Main absorption and disposition parameters using a non-compartmental approach with a log-linear terminal phase assumption. Trapezoidal rule to estimate area under the curve, Terminal phase estimation based on maximising the coefficient of determination. The pharmacokinetic parameters of this trial were Cmax, Tmax, AUCT, AUC0-inf.

Statistical analysis based on a parametric ANOVA model of the pharmacokinetic parameters; two-sided 90% confidence interval of the ratio of geometric means for the Cmax, AUCT and AUC0-inf, based on In-transformed data; non-parametric analysis for Tmax. Level of significance assessed at the two-sided 5% level.

ANOVA model:

- fixed factors: sequence, period, treatment
- random factor: subject (nested within sequence)

Criteria for Bioequivalence

The following standards for bioequivalence were to be applied, based on pioglitazone:

- The 90% confidence interval for the exponential of the difference between the Test and the Reference product for the In-transformed parameters Cmax and AUCT should be between 80 and 125%.

The Cmax and AUCT intra-subject variation following a single dose of appears to be about 30 %. Statistically, given that the expected Test to Reference Cmax and AUCT ratio should fall between 95 and 105%, it was estimated that the lowest number of volunteers to meet the 80-125% confidence interval limits with a statistical power of at least 80% was about 42.

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.

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	1456.3	43.7	1610.6	44.3
ln (C_{max})	7.2055	5.5	7.2893	6.2
T_{max} (hours) *	3.00	39.3	2.05	51.3
AUC_T (ng·h/mL)	16813.3	32.8	17095.8	42.2
ln (AUC_T)	9.6789	3.4	9.6717	4.0
AUC_∞ (ng·h/mL)	17390.1	31.2	17766.3	40.2
ln (AUC_∞)	9.7193	3.1	9.7205	3.6
$AUC_{T/\infty}$ (%)	97.56	1.9	97.08	2.6
K_{el} ($hour^{-1}$)	0.0576	51.8	0.0612	45.1
$T½_{el}$ (hours)	15.32	46.1	14.25	58.0

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	31.6	1344.8	1462.9	91.93	82.42	102.54
AUC_T	21.5	15968.7	15856.8	100.71	93.38	108.61

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

The test over reference product mean ratios and their 90% confidence intervals for the plasma pioglitazone pharmacokinetic variables C_{max} and AUC_{0-t} (as measures of the rate and of extent of pioglitazone absorption, respectively) were 91.93 (82.42-102.54) % and 100.71 (93.38-108.61) %, respectively. Median times to reach C_{max} were similar with 3.00 and 2.05 h for test and reference formulation, respectively, and mean half-lives were also similar with 15.32 and 14.25 h for test and reference formulation, respectively.

Safety data

Twenty of the 45 subjects experienced a total of 36 AEs during the study. Thirteen AEs (11 different types) were reported after the single dose administration of the Test product, and 24 AEs (15 different types) were reported after the single dose administration of the Reference product. Thirteen possibly related events [testicular pain, fatigue, somnolence (5 episodes), nausea (3 episodes), dizziness, abdominal pain, and neutrophil count decreased] were unexpected. No serious AEs were recorded in this study. One adverse event (neutrophils count decreased associated with post-study laboratory test

results) was imputed to both formulations. Three subjects administered the reference product experienced dizziness.

Conclusions

Based on the presented bioequivalence studies Pioglitazone ratiopharm 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

Two bioequivalence studies were provided for Pioglitazone ratiopharm application. The bioequivalent studies 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 $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ 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 studies showed that the 90% confidence intervals of the test/reference (T/R) ratio lie within the prospectively defined acceptance criteria of 80-125% for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max}. The applicant has documented bioequivalence between Actos (marketed by Takeda Global Research and Development Centre (Europe) Ltd) and Pioglitazone ratiopharm 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. 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.

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 Actos tablets. The reference product Actos is indicated "for the treatment of type 2 diabetes mellitus:

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."

From a quality perspective, Pioglitazone ratiopharm 15 mg, 30 mg or 45 mg tablets is similar to Actos as it is, like Actos, presented as immediate release tablets and contains the same excipients. The quality of the active substance is adequately controlled and all excipients comply with the Ph.Eur. The finished product manufacturing process shows to be capable of consistently producing tablets that meet the finished product specifications and appropriate packaging is used to ensure the product remains stable within the agreed shelf-life.

No nonclinical studies have been provided for this generic 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.

Two bioequivalence studies form the pivotal basis with a cross-over design under fasting conditions. The study designs were considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements. Choice of dose, sampling points, overall sampling times as well as wash-out periods were adequate. The analytical methods were validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulations of Pioglitazone ratiopharm 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 and available 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 in the framework of the procedures under Article 20 of Regulation 726/2004 for pioglitazone containing medicinal products, the CHMP considers by majority that the benefit-risk balance of Pioglitazone ratiopharm in the indication below:

"in the treatment of type 2 diabetes mellitus:

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."

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 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 Ratiopharm (EMEA/H/C/002260)

Divergent statement

We have a divergent opinion on the above mentioned Marketing Authorisations from that which has been adopted by the CHMP during its July 2011 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:

Philippe Lechat (FR)	21 July 2011	Signature: ……
Martina Weise (DE)	21 July 2011	Signature: ……
Nela Vilceanu (RO)	21 July 2011	Signature: ……
Christian Schneider (Co-opted)	21 July 2011	Signature: ……