



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

Paglitaz

International non proprietary name: pioglitazone

Procedure No. EMEA/H/C/002309

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



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1 Background information on the procedure

1.1 Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 27 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Paglitaz, through the centralised procedure falling within the scope of the Article 3 (3) – ‘Generic of a Centrally authorised product’ of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 March 2010.

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

The applicant applied for the following indication:

Pioglitazone 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 in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

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

The legal basis for this application refers to:

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

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

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Glustin 15 mg, 30 mg, 45 mg tablets

- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd
- Date of authorisation: 11/10/2000
- Marketing authorisation granted by:
 - Community

Community Marketing authorisation number:

Glustin 15 mg tablets EU/1/00/151/001-003, 007, 014-016, 023

Glustin 30 mg tablets EU/1/00/151/004-006, 008, 017-019, 024

Glustin 45 mg tablets EU/1/00/151/009-013, 020-022

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

- Product name, strength, pharmaceutical form: Glustin 15 mg, 30 mg, 45 mg tablets
- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd
- Date of authorisation: 11/10/2000
- Marketing authorisation granted by:
 - Community
- Community Marketing authorisation number:

Glustin 15 mg tablets EU/1/00/151/001-003, 007, 014-016, 023

Glustin 30 mg tablets EU/1/00/151/004-006, 008, 017-019, 024

Glustin 45 mg tablets EU/1/00/151/009-013, 020-022

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

- Product name, strength, pharmaceutical form: Actos 45 mg tablets
- Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd
- Date of authorisation: 13/10/2000
- Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number(s):
 - EU/1/00/150/011-015, 022-024
 - Member state source:
- Bioavailability study number: Study 09-267

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2 Steps taken for the assessment of the product

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

Rapporteur: Dr 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 10 February 2011.
- During the meeting on 14-17 March 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 March 2011.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 29 March 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 May 2011.
- During the CHMP meeting on 16-19 May 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 23rd May 2011.
- Due to the pending Article 20 Referral procedure and in the light of the overall data submitted and the scientific discussion within the Committee during the meeting on 18-21 July 2011, the CHMP issued a positive opinion for granting a Marketing Authorisation to Paglitaz on 21 July 2011.
- 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 product. During the meeting on 16-19 January 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive revised opinion for granting a Marketing Authorisation to Paglitaz. Divergent positions are included.

Medicinal product no longer authorised

2 Scientific discussion

2.1 Introduction

This centralised application is submitted by Krka, d.d. Novo mesto for Paglitaz 15 mg, 30 mg, 45 mg Tablets according to regulation EC No 726/2004, article 3(3)- generic of a centrally authorised product. It is submitted in accordance with article 10(1) of 2001/83/EC. The reference medicinal products are Glustin 15 mg, 30 mg, 45 mg Tablets authorised by EMA on 11 October 2000. Bioequivalence has been demonstrated against Actos 45 mg tablets authorised by EMA on 13 October 2000. These are identical duplicate products marketed by Takeda.

In addition to the presentations authorised for Glustin, the applicant has added the 60 tablets presentations for the 15 mg tablets, the 30 mg tablets and the 45 mg tablets. The proposed pack sizes are consistent with the dosage regimen and duration of use.

Pioglitazone hydrochloride belongs to the class of thiazolidinediones (ATC code: A10BG03). The proposed indication 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 in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

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

The product is intended for use in the adult population only.

Pioglitazone is a high affinity ligand for PPAR γ , a member of the nuclear receptor superfamily of ligand-activated transcription factors. The most relevant mode of pioglitazone action seem to be the activation of this receptor. Once activated, PPAR γ forms a heterodimer with another nuclear receptor, the retinoid-X receptor. This heterodimer then binds to specific DNA sequences and regulates the transcriptional activity of target genes that play a role in the metabolism of glucose and lipids by

regulating synthesis and expression of cellular glucose and fatty acid transporters. Pioglitazone is dependent on the presence of insulin in order to exert its beneficial effects. The activation of PPAR γ by pioglitazone leads to increased peripheral, hepatic and adipocyte insulin sensitivity. By reducing insulin resistance, pioglitazone lowers fasting and postprandial blood glucose concentrations, circulating free fatty acids and insulin levels, and also hepatic glucose production may decline.

The glucose-lowering effect of pioglitazone in patients with non-insulin dependent diabetes mellitus is also related to its ability to reduce insulin resistance in skeletal muscle. PPAR- γ activation also stimulates differentiation of pre-adipocytes and bone marrow stromal cells into mature adipocytes. Barring the beneficial effects on glycaemic control, insulin levels and function and free fatty acids, pioglitazone also confers benefits in terms of other lipid parameters, hsCRP, MMP-9, MCP-1 and adiponectin.

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

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

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

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

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

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

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

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

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

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

Pioglitazone is contraindicated in diabetic ketoacidosis.

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

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

2.2 Quality aspects

2.2.1 Introduction

Paglitaz are tablets that exist in 3 strengths namely 15 mg, 30 mg and 45 mg differentiated by their size and strengths 15 mg and 45 mg further by engravings.

The formulation contains pioglitazone hydrochloride as the active substance and the following common compendial excipients: lactose monohydrate (diluent), croscarmellose sodium (disintegrant), hydroxypropylcellulose (binder), magnesium stearate (lubricant).

The proposed packaging for the finished tablets consists of blisters: OPA/Al/PVC foil - aluminium foil blisters placed in a printed carton.

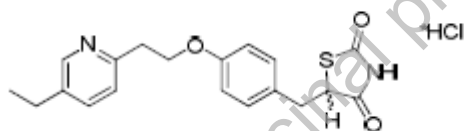
2.2.2 Active Substance

Pioglitazone INN is a known active substance. There is no monograph in the European Pharmacopoeia, but a draft monograph has been published in Pharmedica 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.

Physico-chemical characterisation of Pioglitazone hydrochloride (see its structure below) has been adequately conducted and tests included appearance (white to almost white powder), solubility in various solvents and pH, melting point, pKa, pH, polymorphism (one polymorphic form is consistently produced), isomerism (a racemic mixture is routinely obtained), hygroscopicity (non hygroscopic), particle size (controlled)



Manufacture

The synthesis of pioglitazone hydrochloride has been well described. It can be summarised in six steps. Five of them are synthesis steps and the last one is the crystallisation of the final product.

The main intermediate can be prepared by two different processes (process 1 and process 2). These processes have the same first reaction steps, but differ slightly in the reaction and isolation conditions. The other steps of the synthesis are the same for both processes. In the last step pioglitazone hydrochloride is crystallised to prepare the final active substance.

A flow chart and a detailed description have been provided.

Starting materials have been well characterised along with a brief description of the analytical methods used and a summary of the validation of the methods used for their control.

Specifications for all other solvents and reagents have been provided and are acceptable. The reagents and solvents are suitably controlled for the stage of use.

No specific critical steps have been identified. Seven in-process controls are applied in the synthesis of pioglitazone hydrochloride, but only one intermediate is isolated and controlled with adequate specification.

The in-process control specifications are the same irrespective of whether process 1 or 2 is used. The methods used for the in-process controls and for the control of the intermediate have been provided and validated.

No process validation data have been provided. It has been confirmed that process validation will be performed before launching the product. As this is not a sterile active this is acceptable.

A very brief description of the development of the manufacturing process has been provided. It is stated that minor changes were made during the scale development, but these did not influence the yield or quality of the substance. This is considered acceptable.

Characterisation

The chemical structure of Pioglitazone hydrochloride has been determined by ^1H -NMR, ^{13}C -NMR, FTIR, elemental analysis, mass spectrometry, melting point and X-ray diffraction. Spectra have been provided. Polymorphism was confirmed by X-ray diffraction. It has been shown that the manufacturing process produces consistently the same polymorphic form

Impurities

The extensive discussion on potential impurities included synthetic impurities, residual solvents, inorganic impurities and metal catalysts (although no metal catalysts were used). The synthetic process was also evaluated regarding genotoxic impurities and it was demonstrated that their levels were below the authorised limits in the final active substance. All the impurities levels including residual solvents were in accordance with ICH limits.

Specification

A European Pharmacopoeia monograph for Pioglitazone Hydrochloride has been drafted and published in PharmEuropa 22.4. A monograph for the active substance Pioglitazone Hydrochloride will also be published in USP 34.

As the official monograph is not yet available, pioglitazone is analyzed by the active substance manufacturer as per in-house specification. Parameters tested included: appearance (visual method), solubility (Ph.Eur), identification (Infra-Red and chloride method), sulphated ash (Ph.Eur.), loss on drying (Ph.Eur), heavy metals (Ph.Eur.), specific optical rotation (Ph.Eur), related substances (High Pressure Liquid Chromatography HPLC), pioglitazone hydrochloride assay (HPLC), particle size (laser diffraction), residual solvents (GC), genotoxic impurities (HPLC).

Solubility, identity by IR, identity of chlorides, sulphated ash, loss on drying and heavy metals were tested using Ph. Eur. methods. Validation was not required for simple Ph. Eur. methods (such as solubility, sulphated ash, loss on drying, heavy metals),

The non-compendial methods such as the method used for related substances and pioglitazone content have been adequately described and validated in accordance with ICH guidelines.

The active substance specification has been appropriately justified and found acceptable.

Batch Analysis

Batch analysis data have been provided for 4 batches of Pioglitazone hydrochloride. All results are within the specifications and are acceptable.

Container Closure System

The active substance is packed in two low density polyethylene (LDPE) bags inside a carton drum. Specifications have been provided for the LDPE bags including the IR spectra. The Certificates of Analysis confirms that they comply with the specifications. A statement confirming compliance with Directive 2002/72/ EC as amended and the Ph. Eur. Monograph on olefins has also been provided.

Stability

Stability studies have been conducted on three production scale batches under ICH conditions (24 months at 25°C/60% RH, 12 months at 30°C/65% RH and 6 months at 40°C/75% RH). Photostability testing has also been carried out.

Tests for stability testing include: appearance, loss on drying, Pioglitazone content and related substances. This is acceptable as these are the stability indicating parameters.

No increase in impurities has been observed and no significant change were noticed. Results indicate that Pioglitazone hydrochloride complies with the end-of-shelf life specifications under all tested storage conditions.

The available stability data support a justified retest period, with no special storage conditions.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The drug product is presented as white to almost white round tablets with bevelled edges. The three different strengths (15 mg, 30 mg, 45 mg) are differentiated by the size of the tablets and strengths 15 mg and 45 mg by engravings.

The formulation contains pioglitazone hydrochloride as the active substance and the following common compendial excipients: lactose monohydrate (diluent), croscarmellose sodium (disintegrant), hydroxypropylcellulose (binder), magnesium stearate (lubricant).

The development of the formulation has been adequately described.

During the development, in comparison to the reference product, carmellose calcium was replaced by croscarmellose sodium and hypromellose by hypromellose. Compatibility of the active substance with the excipients has been demonstrated and confirmed during ICH stability studies.

The tablets are kept in blisters made of OPA/AL/PVC foil and aluminium foil inside a printed carton

Manufacture of the product

During the formulation development both direct compression and wet granulation were compared and wet granulation selected since it was found to give better physical properties.

The qualitative and quantitative composition of the 15mg, 30mg and 45mg tablets is the same with the same ratio between active ingredient and all the excipients. The manufacturer and the manufacturing process are the same for all strengths.

The effect of particle size was investigated. Dissolution profiles of batches manufactured using pioglitazone of different particle sizes were compared to the bioequivalence test and reference products and similar profiles were observed.

Comparative dissolution studies have been conducted against the reference product in three different pH. All strengths showed a dissolution of 85% in 15 min. The results were satisfactory and showed the similarity of dissolution profiles between the tested product and the reference product. The release and shelf life specification are set based on the dissolution data of the biobatches.

A biowaiver was requested for all strengths in accordance with the "Guideline on the investigation of Bioequivalence" (CPMP/QWP/EWP/EWP/1401/98 rev 1) and it was agreed that the criteria were fulfilled to grant this biowaiver.

The choice of the container closure system was adequately justified and stability results indicate that the packaging material is suitable for this finished product.

The impurity profile in the test product was compared against those of the reference product and found comparable. Results were within the specification in line with ICH thresholds. The impurity levels seen in both products were very low and the results obtained for the test products are not higher than those observed in the reference products. All impurities found in Paglitaz have been qualified and present no toxicological concern in the levels observed.

Description of the manufacturing process and process control

The manufacturing process is relatively simple and consists of mixing of excipients, granulation of excipients, addition of active substance and disintegrant, mixing with lubricant and compression.

A flow chart detailing the different steps is provided. In-process controls are performed on the dry granulate, the compression mixture and the tablets following compression.

Sufficient information has been provided on the equipment used and the manufacturing conditions.

Information is also provided on the packaging process. Blister tightness is controlled using the vacuum test. The information on the packaging process is acceptable.

Controls of critical steps and intermediates

Three critical steps have been identified (granulate, compression mixture and compressed tablets) and adequate controls put in place. The critical steps cover all of the parameters relevant for immediate release tablets.

Process validation

Process validation has been satisfactorily performed on three pilot scale batches of each strength. Content uniformity in the compression mixture and parameters related to the tableting process were investigated.

The results were in line with the pre-defined criteria and were acceptable. A validation protocol has been provided and is acceptable.

Control of Excipients

All excipients used in the manufacture of pioglitazone hydrochloride tablets comply with their respective Ph. Eur. monographs. Satisfactory certificates of analysis have been provided.

Statements have been provided from all suppliers certifying that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the lactose complies with the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev2). Lactose monohydrate is not considered to pose a TSE risk.

A statement has also been provided to confirm that magnesium stearate is of vegetable origin.

Product Specification

Adequate release and shelf-life specifications for the 15 mg, 30 mg and 45 mg tablets have been provided and include parameters such as: appearance (visual), identification of pioglitazone (HPLC), identification of chlorides (Ph. Eur.), related substances (HPLC), dissolution (Ph.Eur.), pioglitazone content (HPLC), uniformity of content (Ph.Eur.), microbial purity (Ph.Eur.).

Descriptions of the analytical procedures used for control of the drug product have been provided. The validation of the analytical procedures met the requirements of ICH Q2 (R1). The process validation scheme to be followed for the commercial batches has been provided and is acceptable.

Batch analysis data have been provided on 5 batches of each strength. The batch sizes were at least pilot scale. All of the results comply with the specifications and confirm the consistency and uniformity of the product.

A justification has been provided for all of the tests and limits included in the specification. The content specification at release and shelf life is in line with ICH Q6A and usual requirements for tablets. The dissolution specification is in line with the results of the bio-batch and is acceptable. Uniformity of dosage units and microbiological purity are tested in line with the Ph. Eur. Impurity specifications are in line with ICH identification limits and are acceptable.

The container closure system consists of cold formed OPA/Al/PVC foil and aluminium foil. The blister trays are cold-formed from OPA/Al/PVC foil and after the tablets are introduced the aluminium foil is heat-sealed onto the trays.

Specifications for the OPA/Al/PVC foil and aluminium foil have been provided. The specifications include identification by FT-IR and reference spectra have been provided. Confirmation of compliance with Ph Eur. 3.1.11 (materials based on non-plasticised poly(vinyl chloride) for containers for dry dosage forms for oral administration) for the OPA/Al/PVC foil and directive 2002/72/EC for both foils has been provided. The primary packaging for the bulk product is polyethylene bags. Compliance with food contact requirements has been confirmed.

Stability of the product

Stability testing was performed on three pilot scale batches of each strength kept in the commercial packaging. The batches were kept under long-term conditions (up to 60 months at $25\pm 2^{\circ}\text{C}/60\pm 5\% \text{ RH}$) and under accelerated conditions (6 months at $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{ RH}$). The testing conditions and intervals were according to ICH Q1A (R2).

The following parameters were tested during stability studies: appearance, pioglitazone content, related substances, water content (for information), hardness (for information), dissolution, microbiological purity. The analytical methods were the same as those used for the control of the finished product.

All results comply with the specification and no trends have been observed. No impurities have been detected above the reporting limit.

Based on the stability data, the results support the shelf life and storage conditions as defined in the SmPC.'

2.2.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance pioglitazone and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

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.

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

Ecotoxicity/ environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Paglitaz tablets manufactured by Krka, d.d., Novo mesto is considered unlikely to result in any significant increase in the combined sales volumes for all pioglitazone containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4 Clinical Aspects

2.4.1 Introduction

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

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of pioglitazone based on published literature; this was considered acceptable. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1*) in its current version is of particular relevance.

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

As this marketing authorisation application for pioglitazone, manufactured by KRKA d.d., Novo mesto, Slovenia is based on the "essential similarity" claim, the applicant has performed a clinical study to establish the bioequivalence of Pioglitazone 45 mg tablets, produced by KRKA d. d. and a reference formulation of pioglitazone produced by Takeda. For additional strengths, i.e. Pioglitazone hydrochloride 15 mg tablets and Pioglitazone hydrochloride 30 mg tablets, a biowaiver was claimed based on the justification presented in the dossier and based on the following criteria:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths
- Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing

The selection of the 45 mg dose to establish bioequivalence is in line with the Questions and Answers on the Bioavailability and Bioequivalence guideline EMEA/CHMP/EWP/40326/2006, which in general recommends performance of the bioequivalence study at the highest strength. In addition clinical safety concerns do not prevent the use of the highest strength in healthy volunteers. The biowaiver was granted for the lower strengths.

Clinical studies

To support the application, the applicant has submitted one single bioequivalence study (study code 09-267).

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design; Type of Control	Test Product(s); Dosage Regimen; Rout of Administration	No. of Subjects	Healthy Subjects/ Diagnosis Of Patients	Duration of Treatment	Study Status; Type of report
BE	09-267	Section 5.3.1.2.	Assessment of single-dose relative bioavailability of two tablet formulations after administration under fasting conditions	Crossover; Fasting state with a 2-week washout period	Test Pioglitazone 45 mg tablets Reference Actos® 45 mg tablets	40 (38)	Healthy subjects	Single Dose	Complete Full

2.4.2 Pharmacokinetics

Methods

Study design

The study was "laboratory-blinded", randomised, single-dose with a 2 period 2 sequence cross-over design and was performed in healthy male volunteers under fasting conditions to evaluate and compare the relative bioavailability and therefore the bioequivalence of two different formulations of pioglitazone. Male subjects, aged 18 – 55 with a body mass index within 18.5 and 29 kg/m² were studied.

A single oral dose 45 mg of each formulation was administered to subjects after an overnight fast in each period in a total of two periods. Subjects were administered 60ml of 25% glucose solution approximately 1,2 and 4 hours after dosing to minimise hypoglycaemic effects.

The tested bioequivalence was based on plasma drug levels analysis of pioglitazone. Individual concentrations of pioglitazone and the metabolite were measured in plasma. Blood samples were withdrawn pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, 48, 60 and 72 hours post-dose, after each administration.

There was a 14 calendar days wash-out between the two periods (corresponding to more than 10 times the expected half lives of the substances to be measured).

The open labelled, cross over, single dose design is considered acceptable by the CHMP. A fasting study is appropriate and in accordance with the current bioequivalence guidelines CPMP/EWP/QWP/1401/98 Rev.1 as there is no food effect. The washout period was sufficient long. Also the sampling frequency was sufficient. The sampling was planned to provide a reliable estimate of the extent of absorption of pioglitazone as well as the terminal half life and to ensure that AUC_t was a least 80% of the AUC extrapolated to infinity.

The selection of the highest dosage strength is in agreement with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, which in general recommends performance of bioequivalence study at the highest strength. In addition, clinical safety concerns do not prevent the use of the highest strength in healthy volunteers.

The study was complying with GCP, as claimed by the applicant.

Test and reference products

The bioavailability of Pioglitazone 45 mg tablets manufactured by Krka d.d., further on referred to as test formulation, was assessed in comparison to the reference product Actos (pioglitazone) 45 mg tablets, manufactured by Takeda Ireland Limited, Ireland and obtained on the EU market.

Population studied

Male volunteers, non or ex-smokers, of at least 18 years of age but not older than 55 years with a BMI greater than or equal to 18.5 and below 29kg/m².

Out of 40 subjects enrolled, 38 have concluded both treatment periods and were analysed, while 2 subjects withdrew their consent during the study. These two drop outs were not due to medical reasons.

The population studied is considered adequate by CHMP.

The exclusion and inclusion criteria are acceptable and in line with the requirements of the 'Guideline on the Investigation of Bioequivalence' (Doc. Ref.: CPMP/QWP/ EWP/1401/98 Rev.1, 20 January 2010).

Analytical methods

The bioequivalence study was conducted according to the CPMP Guideline on the investigation of bioequivalence. Plasma samples obtained in the bioequivalence study were analysed for pioglitazone and hydroxy pioglitazone by a validated LC-MS/MS in one analytical run.

For both analytes calibration curve was linear in the applied concentration range.

A comparison of the measured quality control sample (QCs) values with the nominal concentrations was used for the estimation of analytical precision and accuracy.

The results were considered to represent an acceptable level of method repeatability during the present bioequivalence study.

Pharmacokinetic Variables

On the basis of individual plasma concentration/time profiles pharmacokinetic parameters C_{max} , t_{max} , k_{el} and $t_{1/2}$ for both analytes, AUCt and AUCi for pioglitazone and AUC_{0-72h} for M-IV were determined for both formulations.

Test for bioequivalence included an analysis of variance (ANOVA) for AUCt, AUCi and C_{max} parameters of pioglitazone and AUC_{0-72h} and C_{max} parameters of M-IV and followed by the calculation of the 90% confidence intervals for the ratio of test/reference means.

The Pharmacokinetic variables were considered appropriate by the CHMP.

Statistical methods

On the basis of individual plasma concentration/time profiles pharmacokinetic parameters C_{max} , t_{max} , k_{el} and $t_{1/2}$ for both analytes, AUCt and AUCi for pioglitazone and AUC_{0-72h} for M-IV were determined for both formulations.

Test for bioequivalence included an analysis of variance (ANOVA) for AUCt, AUCi and C_{max} parameters of pioglitazone and AUC_{0-72h} and C_{max} parameters of M-IV and followed by the calculation of the 90% confidence intervals for the ratio of test/reference means. The data was ln-transformed prior to analysis. A non-parametric test was used for the untransformed t_{max} parameter.

Statistical inference of pioglitazone was based on a bioequivalence approach using the following standards: The ratio of geometric LS means with corresponding 90% confidence interval calculated from the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max} and AUCt should all be within the 80.00 to 125.00% bioequivalence range. Pharmacokinetic data for M-IV were presented for information purposes only.

The statistical evaluation was considered appropriate by the CHMP.

Results

Out of 40 subjects enrolled, 38 have concluded both treatment periods and were analysed, while 2 subjects withdrew their consent during the study. These two drop outs were not due to medical reasons.

Summary of Main Study Results – Pioglitazone

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C _{max} (ng/mL)	1264.8	46.0	1282.6	35.7
ln (C _{max})	7.0257	7.5	7.0827	5.9
T _{max} (hours) [§]	2.00	55.9	3.00	52.2
AUC _T (ng·h/mL)	14369.7	47.9	16163.9	42.9
ln (AUC _T)	9.4715	4.9	9.6137	4.1
AUC _∞ (ng·h/mL)	14646.6	47.0	16503.2	41.9
ln (AUC _∞)	9.4947	4.8	9.6383	4.0
AUC _{T/∞} (%)	97.72	1.6	97.59	1.7
K _{el} (hours ⁻¹)	0.0736	26.2	0.0746	23.3
T _{1/2el} (hours)	10.08	27.1	9.88	27.1

For Tmax the median is presented and the statistical analysis is based on a non-parametric approach.

Comparison of Results with Standards for Bioequivalence - Pioglitazone

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C _{max}	29.1	1124.1	1196.9	93.92	84.10	104.89
AUC _T	19.8	13044.8	15067.0	86.58	80.23	93.43

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

There were no significant protocol deviations. There were 37 blood sampling deviations but it is stated that for deviations greater than or equal to 2 minutes, it is stated that they were adjusted to reflect actual sampling time. Deviations were mostly 3 – 5 minutes but individual deviations of up to 18, 21, 26 and 41 minutes were noted.

The mean C_{max} were respectively 1264.8 ng/mL and 1282.6 ng/mL for the test and reference formulations and the test to reference C_{max} ratio of geometric LSmeans was 93.925 (90% CI: 84.10 to 104.89%).

The mean AUC_t were respectively 1436.7ng.h/mL and 16163.9ng.h/mL for the test and reference formulations. The test to reference AUC_t ratio of geometric LSmeans was 86.58% (90% CI: 80.23 to 93.43%).

The results therefore suggest that the test formulation is bioequivalent to Actos.

Safety data

There were twenty nine adverse events recorded during the study in fourteen subjects. The incidence of the events and their profile did not indicate any significant differences between the two formulations. There were no cases of hypoglycaemia.

Four possibly drug related adverse events (constipation, a sensation of fever and two cases of nausea) were unexpected. There were no cases of serious adverse events.

Conclusions

The applicant has performed an appropriate pharmacokinetic study in 38 male subjects. The study design was appropriate with an acceptable wash out period. The chosen strength is appropriate.

Inclusion/exclusion criteria were appropriate. Timing of samples was acceptable.

The pharmacokinetic parameters chosen are in accord with the recommendations of the bioequivalence guidance.

Two subjects withdrew for personal reasons and both received Actos 45mg in period 1.

There were no significant protocol deviations.

The mean C_{max} were respectively 1264.8 ng/mL and 1282.6 ng/mL for the test and reference formulations and the test to reference C_{max} ratio of geometric LSmeans was 93.925 (90% CI: 84.10 to 104.89%).

The mean AUC_t were respectively 1436.7ng.h/mL and 16163.9ng.h/mL for the test and reference formulations. The test to reference AUC_t ratio of geometric LSmeans was 86.58% (90% CI: 80.23 to 93.43%).

The results therefore suggest that the test formulation is bioequivalent to Actos.

Based on the presented bioequivalence study, Paglitaz is considered bioequivalent with Actos.

The applicant has provided an appropriate request for biowaiver.

The results of study 09-267 (study code) with 45mg formulation can be extrapolated to other strengths 15 and 30 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

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

The results of study 09-267 (study code) confirmed that the test formulation is bioequivalent to Actos.

2.4.6 Conclusions on clinical aspects

The efficacy and safety profile of pioglitazone in the indication claimed for Paglitaz (i.e. treatment of type 2 diabetes) is well known and no additional clinical studies are needed.

A bioequivalence study was conducted and confirmed that the test product (pioglitazone 45 mg tablets, manufactured by Krka d.d.) is bioequivalent to the Reference formulation (Actos 45 mg tablets, manufactured by Takeda Ireland Limited, Ireland) with respect to rate and extent of availability.

The recommended dosage and method of administration of the generic product Paglitaz 15 mg, 30 mg and 45 mg tablets is the same as that recommended for the reference product Glustin 15 mg, 30 mg and 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 on 27 October 2010. However taking into account the outcome of the Article 20 procedure on already authorised pioglitazone containing products and the potential increased risk of bladder cancer, the MAH shall submit within one month of the Commission Decision a risk management plan which will incorporate risk minimisation measures, as detailed in the conditions or restrictions with regard to the safe and effective use of the medicinal product in Annex II, in line with those required for the reference medicinal product.

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

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

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (Pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSUR cycle

The PSUR cycle for the product will follow the PSUR submission schedule of the reference medicinal product Glustin, 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 pioglitazone oral tablets. The reference product Glustin 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 in adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

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

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.

The pivotal basis forms a bioequivalence study with a "laboratory-blinded", randomised, single-dose with a 2 period 2 sequence cross-over design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pioglitazone 45 mg tablets met the protocol-defined criteria for bioequivalence when compared with the Actos 45 mg tablets. The point estimates and their 90% confidence intervals for the parameters $AUC_{0-t_{tr}}$, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

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

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

4 Recommendation

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

Medicinal product no longer authorised

Appendix I

Divergent positions

Medicinal product no longer authorised

Paglitaz (EMA/H/C/2309)

Divergent statement

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

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

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