

## PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Pioglitazon Sandoz 15 mg, 30 mg and 45 mg, tablets  
Sandoz B.V., the Netherlands**

**pioglitazone (as hydrochloride)**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2058/001-003/DC  
Registration number in the Netherlands: RVG 108641-108643**

**29 May 2012**

Pharmacotherapeutic group:	blood glucose lowering drugs, excl. insulins - thiazolidinediones
ATC code:	A10BG03
Route of administration:	oral
Therapeutic indication:	type 2 diabetes mellitus as mono, dual or triple oral therapy (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	18 October 2011
Concerned Member States:	Decentralised procedure with CY, DE, EE, EL, ES, FI, FR, IT, LT, LV, PT, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Pioglitazon Sandoz 15 mg, 30 mg and 45 mg, tablets from Sandoz B.V. The date of authorisation was on 18 October 2011 in the Netherlands.

The product 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 (see section 4.4 of the approved SPC).

A comprehensive description of the indications and posology is given in the SPC.

Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Actos 15 mg, 30 mg and 45 mg tablets and Glustin 15 mg, 30 mg and 45 mg tablets (EU/1/00/150 and EU/1/00/151), which have been registered in the EEA by Takeda Global Research and Development Centre (Europe) Ltd since 13 October 2000 for the 15 and 30 mg, and 16 September 2003 for the 45 mg strength.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the

pharmacokinetic profile of the reference product Actos 45 mg tablets, registered in the EEA and obtained from the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

## II SCIENTIFIC OVERVIEW AND DISCUSSION

### II.1 Quality aspects

#### **Compliance with Good Manufacturing Practice**

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

#### **Active substance**

The active substance is pioglitazone hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.\*). The active substance is a white to off-white powder, which is practically insoluble in water. The compound is synthesized as a racemic mixture and as polymorphic form I.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

#### Manufacturing process

The manufacturing process of pioglitazone hydrochloride consists of six steps. No class I organic solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents, for both manufacturers.

#### Quality control of drug substance

The drug substance specification of the MAH is mainly based on the specifications of the suppliers with additional requirements for particle size and identification. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches.

#### Stability of drug substance

For one manufacturer, stability data on the active substance have been provided for six full-scale batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). The proposed retest period of 36 months and storage condition 'Store below 30°C' were granted.

For the other supplier, stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months), and for one full-scale batch stored only at 25°C/60% RH (9 months). Based on these data, the proposed retest period of 3 years without any special storage requirements is justified.

\* *Ph.Eur.* is an official handbook (*pharmacopoeia*) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

## Medicinal Product

### Composition

Pioglitazon Sandoz 15 mg is a white, round tablet, with imprint "PGT 15" on one side and with score line on both sides. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Pioglitazon Sandoz 30 mg is a white, round tablet, with imprint "PGT 30" on one side and with score line on both sides. The tablet can be divided into equal halves.

Pioglitazon Sandoz 45 mg is a white, round tablet, with imprint "PGT 45" on one side and with three-part score line on the other side. The tablet can be divided into three equal parts.

The tablets are packed in Al/Al blisters.

The excipients are: lactose monohydrate, hydroxypropylcellulose, carmellose calcium, magnesium stearate.

The three strengths are fully dose proportional.

### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies regarded the characterisation of the active substance, development of a dissolution method and the comparison of dissolution profiles with the reference product. A bioequivalence study was performed with the highest strength of drug product. The test batch used in the BE study was manufactured according to the finalized manufacturing process and composition.

The tablets bear score lines. Breakability into equal parts has been adequately demonstrated for all three strengths. However, as there is no 7.5 mg dose requirement, this is not included in the SPC for the 15 mg. The pharmaceutical development of the product has been adequately performed.

### Manufacturing process

The manufacturing process mainly consists of dry mixing, wet granulation, drying, blending and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three production scale batches of the 15 mg and 30 mg strength and on four full-scale batches of the 45 mg strength.

The product is manufactured using conventional manufacturing techniques.

### Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

### Quality control of drug product

The product specification includes tests for description, water content, identification, assay, uniformity of dosage units, dissolution, related substances and microbial examination. The release and shelf-life limits are identical.

The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for three production-scale batches, demonstrating compliance with the release specification.

### Stability of drug product

Stability data on the product has been provided for four production-scale batches per strength stored at 25°C/60% RH (up to 36 months), 30°C/65% RH (up to 36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-Al blisters. No trends or changes are seen at all three storage conditions.

A photostability study was carried out on two batches of tablets packed in PVC/PVDC-Alu. The product was shown to be photostable. Based on the data provided, a shelf-life of 2 years was granted without any special storage requirements.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only lactose monohydrate is of animal origin. Magnesium stearate is of vegetable origin. Lactose monohydrate is produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption, so there is no TSE risk.

## II.2 Non-clinical aspects

This product is a generic formulation of Actos/Glustin, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

### Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pioglitazone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Pioglitazone is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Pioglitazon Sandoz 45 mg (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Actos 45 mg tablets (Takeda Ireland Limited, Ireland).

### *The choice of the reference product*

The choice of the reference product in the bioequivalence study is justified, as the product has been registered through a centralised procedure. It is therefore considered identical across the EEA member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

### *Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy subjects (22 males and 20 females), aged 22-53 years. Each subject received a single dose (45 mg) of one of the 2 pioglitazone formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 8 hours. Subjects were served a controlled meal not less than 4 hours post-dose, and at appropriate times thereafter, in each period. With the exception of the volume administered at the time of dosing and for glucose solution (given only if subjects were hypoglycaemic), no fluids were allowed from 1 hour before dosing until 1 hour post-dose. Water was provided *ad libitum* at all other times. There were 2 dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose and at 0.3, 0.67, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.3, 3.7, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

### *Analytical/statistical methods*

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

### *Results*

All 42 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of pioglitazone under fasted conditions.

Treatment N=42	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	17047 $\pm$ 5546	17719 $\pm$ 5530	1472 $\pm$ 433	2.33 (0.67-4.5)	12.8 $\pm$ 5.8
<b>Reference</b>	16463 $\pm$ 5099	17201 $\pm$ 5119	1530 $\pm$ 492	1.67 (0.67-5)	10.6 $\pm$ 4.2
<b>*Ratio (90% CI)</b>	1.03 (0.97-1.09)	1.03 (0.97-1.09)	0.98 (0.91-1.06)	--	--
<b>CV (%)</b>	16.3	15.9	20.9	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of pioglitazone under fasted conditions, it can be concluded that Pioglitazon Sandoz 45 mg Actos 45 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Pioglitazone may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of pioglitazone. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

#### Safety

Overall, a total of 15 treatment-emergent adverse events (TEAEs) were reported by 11 of the 42 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 9 TEAEs reported by 16.7% (n=7) of the 42 subjects who received test and 6 TEAEs reported by 9.5% (n=4) of the 42 subjects who received reference product. No deaths, serious or significant adverse events were reported during this study.

#### Extrapolation to different strengths

The results of the bioequivalence study with 45 mg strength formulation can be extrapolated to the other strengths - 15 and 30 mg -, according to conditions described in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

#### Risk management plan

During the DCP, the MAH submitted an abbreviated RMP which includes also the additional risk minimisation measures to address the identified risks of bladder cancer and heart failure in line with those required for the reference medicinal product. This abbreviated RMP was assessed and approved during the DCP.

**Educational material: Conditions or restrictions with regard to the safe and effective use of the medicinal product**

The MAH committed to submit a proposal for the (national) educational pack, in line with the material for the reference product, targeting all physicians who are expected to prescribe/use Pioglitazone in each member state within one month after the marketing authorisation has been granted in that specific member state. Prior to distribution of the prescriber guide in each Member State, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

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

The Prescriber Guide should highlight the following:

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

**PSURs**

The PSUR submission schedule follows the PSUR submission schedule for the reference medicinal product. The PSUR cycle of the reference product is 6-monthly. The data lock point of the first PSUR will be in January 2012. The PSURs will include detailed reviews of the safety concerns, as agreed for the reference product:

- Cardiac Failure
- Weight Gain and Oedema
- Hepatobiliary Events
- Blood Disorders
- Rhabdomyolysis
- Anaphylactoid Reactions
- Malignancy including Bladder Cancer
- Lactic Acidosis
- Hypoglycaemia
- Macular Oedema
- Bone Fractures
- Cardiac and Cerebrovascular Ischaemia

The MAH submitted a commitment that these safety concerns will be closely monitored and discussed in the PSURs. The MAH also committed to provide meaningful estimates of patient exposure in the context of ongoing risk management for the active substance in the EU in the PSURs.

**Product information**

**SPC**

The SPC is completely in accordance with the text of the reference product Actos, as agreed during the recently finalised review of pioglitazone-containing medicines.

**Readability test**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with two panel members, followed by two rounds with 10 participants each. The leaflet was written and tested in English. The composition of the subject population is acceptable as far as age, gender and education are concerned.

Key messages for safe use of Pioglitazone tablets were identified by the medical writer, by examination of the PL text for information on contraindications, special warnings and precautions, concomitant medication, posology and administration, stopping treatment, use in breast-feeding women and undesirable effects. All questions were designed to determine whether users of this product can identify key information that is necessary to warrant the appropriate use of Pioglitazone tablets. Questions that addressed the same sections of the package leaflet were not asked in a consecutive order to avoid leading of the subjects.

In the test, the subjects received a mock-up of the proposed Pioglitazone tablets PL to read, and then questions were asked designed to determine whether they could:

- (1) locate specific information in the PL and
- (2) understand and explain that information and
- (3) how they would act upon it.

The subject were asked to formulate their responses in their own words

The pilot test showed that the leaflet performed well with most questions being answered with relative ease. Two questions were found to be slightly more difficult and these questions have been amended. It was also suggested that the subheading of “Broken bones” be emboldened as well as “Other diabetic medicine” in Section 4 to make this section more visible. These changes were implemented before the first test round. Following Round 1, no further revisions were required and the mock-up was progressed to Round 2. Following Round 2, also no further revisions were required.

Information was located and understood by at least 90% of the subjects for all 17 questions in both rounds. The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In conclusion, the readability test has been sufficiently performed.



### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pioglitazon Sandoz 15 mg, 30 mg and 45 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Actos 15 mg, 30 mg and 45 mg, and Glustin 15 mg, 30 mg and 45 mg tablets. Actos/Glustin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pioglitazo Sandoz 15 mg, 30 mg and 45 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 September 2011. Pioglitazon Sandoz 15 mg, 30 mg and 45 mg were authorised in the Netherlands on 18 October 2011.

The MAH submitted an abbreviated RMP which includes also the additional risk minimisation measures to address the identified risks in line with those required for the reference medicinal product. The PSUR submission schedule follows the PSUR submission schedule for the reference medicinal product. The PSUR cycle of the reference product is 6-monthly. The data lock point of the first PSUR is January 2012.

The date for the first renewal will be: 22 January 2016.

The following post-approval commitments have been made during the procedure:

#### Pharmacovigilance – educational material

- The MAH committed to submit a proposal for the (national) educational pack, in line with the material for the reference product, targeting all physicians who are expected to prescribe/use Pioglitazone, in each member state within one month after the marketing authorisation has been granted in that specific member state.

## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t <sub>1/2</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

