



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 19 January 2012
EMA/207581/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sepioglin

International nonproprietary name: pioglitazone

Procedure No. EMEA/H/C/002021

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

Medicinal product no longer authorised



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Medicinal product no longer authorised

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Vaia S.A. submitted on 26 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sepioglin, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 October 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 as second or third line treatment of type 2 diabetes mellitus as described below:

as **monotherapy**

- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance,

as **dual oral therapy** in combination with

- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea,

as **triple oral therapy** in combination with

- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance (see section 4.4).

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained (see section 4.4).

The legal basis for this application refers to:

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

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

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
 - Product name, strength, pharmaceutical form: Actos 15, 30 mg tablets
 - Marketing authorisation holder: Takeda Global Research and Development Centre (Europe) Ltd.
 - Date of authorisation: 13 October 2000
 - Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number: EU/1/00/150/001-028
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
 - Product name, strength, pharmaceutical form: Actos, 15, 30, 45 mg tablets
 - Marketing authorisation holder: Takeda Global Research and Development Centre (Europe), Ltd.
 - Date of authorisation: 13 October 2000
 - Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number: EU/1/00/150/012
- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:
 - Product name, strength, pharmaceutical form: Actos 45 mg tablet
 - Marketing authorisation holder: Takeda Global Research and Development Centre (Europe), Ltd.
 - Date of authorisation: 16 September 2003
 - Marketing authorisation granted by:
 - Community
 - Community Marketing authorisation number: EU/1/00/150/012
 - Bioavailability study number: Study code 80222

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2 Steps taken for the assessment of the product

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

Rapporteur: P. Salmon

- The application was received by the EMA on 26 October 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 February 2011.

- During the meeting on 14 – 17 March 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 April 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 06 June 2011
- During the CHMP meeting on 20- 23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 5 August 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 August 2011.
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sepioglin on 22 September 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 authorisation are 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 Sepioglin. Divergent positions are included.

2 Scientific discussion

2.1 Introduction

This product is a generic medicinal product containing pioglitazone as pioglitazone hydrochloride as active substance.

The reference medicinal product is Actos 15, 30, 45 mg tablet.

Pioglitazone is a thiazolidinedione compound that acts as a peroxisome proliferator activating receptor (PPAR)- γ agonist with potential benefits on insulin resistance. Pioglitazone does not stimulate insulin secretion (unlike sulphonylureas), and it does not inhibit glucose absorption (unlike α -glucosidase inhibitors). It depends on the presence of insulin for activity.

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

The approved indication for Sepioglin is identical to the current indication of the reference medicinal product Actos:

"Pioglitazone is indicated as second or third line treatment of type 2 diabetes mellitus as described below:

as **monotherapy**

- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance,

as **dual oral therapy** in combination with

- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea,

as **triple oral therapy** in combination with

- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

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

2.2 Quality aspects

2.2.1 Introduction

The product is presented as tablets containing 15, 30 and 45 mg of pioglitazone hydrochloride as active substance, like the product.

Other ingredients are lactose monohydrate, carmellose calcium, hydroxypropyl cellulose , and magnesium stearate.

The tablets are packed in Aluminium/aluminium blisters.

2.2.2 Active Substance

This medicinal product contains as active substance pioglitazone INN, as the hydrochloride. The chemical name of pioglitazone hydrochloride is (±)-5-[[4-[2-(5-Ethyl-2-pyridinyl)-ethoxy]phenyl]methyl]-2,4-thiazolidinedione hydrochloride. The molecular formula is C₁₉H₂₀N₂O₃S.HCl and the molecular weight is 392.90 g/mol.

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

Pioglitazone hydrochloride is not hygroscopic. It exhibits stereoisomerism due to the presence of one chiral center and is synthesized and used as racemic mixture. The two enantiomers of pioglitazone inter-convert in vivo. No differences were reported in the pharmacological activity between the two enantiomers.

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

Manufacture

At the time of the CHMP opinion, the active substance used for Sepioglin 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). 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, ¹H NMR, ¹³C NMR, MS and UV. The crystalline nature and polymorphism were characterised by DSC and XRD.

Specification

There is no Ph.Eur monograph for pioglitazone hydrochloride and hence the active substance is tested as per in-house specifications. The specifications include tests as: description, solubility (Ph Eur), identification (IR, test for chloride), loss on drying, residue on ignition, heavy metals (Ph.Eur), melting range, particle size, related substances (HPLC), assay (HPLC), residual solvents (GC), dimethyl formamide and methyl acetate content (GC) and specific optical rotation.

The specifications and tests proposed are compliant with the relevant ICH guidelines and general requirements of Ph.Eur. The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data have been provided by the active substance supplier on six batches. All batches were in compliance with the predefined active substance specifications and confirm consistency and uniformity of the active substance manufacture.

Stability

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

Stability studies on the active substance have been performed at long term ($25\pm 2^{\circ}\text{C}/60\pm 5\% \text{ RH}$) and accelerated ($40\pm 2^{\circ}\text{C}/75\pm 5\% \text{ RH}$) 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 ($25^{\circ}\text{C}/60\% \text{ RH}$ for 72 hours), humidity ($25^{\circ}\text{C}/90\% \text{ RH}$ 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 objective was to develop a formulation for oral administration as a generic equivalent to the originator product Actos. The tablet design of the development was to develop weight proportional tablets for all tablet strengths. A compatibility study with the chosen excipients was performed. No issues are likely as the same excipients are present in the reference medicinal product. The excipients, and their proposed levels, were chosen to give appropriate dissolution rate and stability of the finished dosage form, with the ultimate goal being to develop a stable immediate release formulation matching the reference product, both *in-vivo* and *in-vitro*. As the active substance shows linear pharmacokinetics, the applicant has performed only one bioequivalence study with the 45 mg strength. The applicant proposed a biowaver for the two lower product strengths which was supported by dissolution data.

In addition to this bioequivalence study, a comparative dissolution, and comparative assay and impurity profile testing was also performed, in order to demonstrate pharmaceutical equivalence.

All excipients used for the manufacturing of Pioglitazone tablets meet the requirements of the Ph.Eur. and they are tested according to the currently valid monograph.

Standard packaging materials are chosen - the finished product is packaged in OPA/Aluminium/PVC/Aluminium blisters. The blisters are subsequently packed into cardboard boxes. The stability results presented demonstrate that there are no adverse interactions between finished product and the packaging and that the packaging materials offer sufficient protection to the drug product from the external environment.

Adventitious agents

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

Manufacture of the product

The manufacturing process includes wet granulation, tableting and packaging.

The manufacturing process has been validated for pilot scale batches by a number of studies for the major steps of the manufacturing process.

The batch analysis data show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation

Product Specification

The finished product specifications include appropriate tests for appearance, identification (HPLC,UV), average weight, dissolution, uniformity of dosage units (HPLC), uniformity of dosage (HPLC), assay (95.0% - 105.0%, HPLC), related substance, (HPLC), water content (KF), resistance to crushing (Ph Eur), disintegration (Ph Eur), friability (Ph Eur), breakability (Ph Eur), microbiological quality (Ph Eur).

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies were performed on 9 pilot batches in total (3 of each strength). The studies were carried out in accordance with current ICH/CHMP guidelines and the characteristics tested were as presented in the Finished Product Specifications with the addition of hardness and LOD tests which were monitored for information only. Stability data submitted covers long-term up to 36 months at 25°C/60%RH and accelerated 6 months at 40°C/75% RH for the finished product as packaged for sale. 6 months stability data at 25°C/60%RH are presented for bulk tablets. Appropriate stability commitments were provided.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable, and it is concluded that the tablets need to be stored in the original packaging to protect from moisture.

2.2.4 Discussion on chemical, and pharmaceutical aspects

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

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3 Non- Clinical aspects

2.3.1 Introduction

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

2.4 Clinical Aspects

2.4.1 Introduction

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

GCP

The Clinical 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 Specifar, S.A., Greece 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 Specifar, S.A. 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 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 bioequivalence study to demonstrate bioequivalence between their product and the reference product Actos.

Study 80222 was a single centre, 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.

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 80222

Methods

Study design

Study code: 80222

Title of the study: Randomised, Open-Label, 2-Way Crossover, Bioequivalence Study of Pioglitazone 45 mg Tablet and Actos (Reference) Following a 45 mg 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 extent of absorption of a test pioglitazone versus Actos, a reference pioglitazone, under fasting conditions.

Test and reference products

Treatment		
	Test (A)	Reference (B)
Name:	pioglitazone hydrochloride	pioglitazone hydrochloride (Actos®)
Unit dose:	45 mg	45 mg
Regimen:	single dose of 1 x 45 mg tablet per subject in accordance with the randomisation scheme	single dose of 1 x 45 mg tablet per subject in accordance with the randomisation scheme
Lot/Batch No.:	7K22	A440189
Expiry date:	05/2010	07 2010
Manufacturing date:	30.11.2007	Not available
Company Responsible for Manufacturing:	Specifar S.A., Greece	MAH: Takeda Global Research and Development Centre (Europe) Ltd., United Kingdom Distributor: Eli Lilly, Greece

Population(s) studied

A total of 72 healthy adult male (N=36) and female subjects (N=36) aged between 18 and 55 years with a BMI of 19 to 30 kg/m² were enrolled for the study.

Females of child bearing potential were included if they used appropriate methods of contraception.

Sixty-eight (68) subjects completed all treatment phases, and analytical results from these 68 subjects were available for statistical analysis.

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 High Performance Liquid Chromatography / Tandem Mass Spectrometry Method.

Pharmacokinetic Variables

The pharmacokinetic parameters for this study were AUC_{0-t}, AUC_{0-inf}, C_{max}, Residual area, T_{max}, Kel, and T_{1/2el}.

The Pharmacokinetic variables were considered appropriate by the CHMP.

Statistical methods

Pharmacokinetics:

- Parametric ANOVA on C_{max}, AUC_{0-t}, AUC_{0-inf} and T_{1/2} and Kel; geometric confidence intervals for C_{max}, AUC_{0-t} and AUC_{0-inf}; and non-parametric test (Wilcoxon) for T_{max};
- Covariates in the ANOVA model: sequence, subject within sequence, period and treatment;
- Ln-transformed parameters: C_{max}, AUC_{0-t} and AUC_{0-inf}

Criteria for Bioequivalence for pioglitazone:

- 90% geometric confidence intervals of the ration (A/B) of least-squares means from the ANOVA of the ln-transformed C_{max}, AUC_{0-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 $\pm$ SD, t_{max} median) and for the mean ratios of the 90%CI for AUC_{0-t}, AUC_{0-inf}, C_{max} are summarised in the tables below.

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, T_{max}: median, range) for Pioglitazone

Parameters	Test (Pioglitazone HCl (A))			Reference (Actos (B))		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC _{0-t} (ng h/mL)	13538.06	5038.22	37.22	14336.16	5134.72	35.82
AUC _{0-inf} (ng h/mL)	14156.04	5237.19	37.00	15079.69	5660.22	37.54
C _{max} (ng/mL)	1152.93	430.41	37.33	1200.94	422.83	33.63
Residual area (%)	4.55	3.87	84.98	4.61	6.01	130.50
T _{max} (h)	2.18	1.21	55.25	2.17	1.14	52.74
T _{max} * (h)	2.00	2.34	-	2.00	1.67	-
K _{el} (h ⁻¹)	0.0654	0.0272	41.54	0.0677	0.0264	38.94
T _{1/2 el} (h)	13.06	6.86	52.54	12.49	7.45	59.63

* Medians and interquartile ranges are presented.

Table 2: ANOVA 90% Confidence Interval (Ln transformed) and intra-subject CV% for AUC 0-t, AUC 0-inf and C_{max} Pioglitazone and as supportive information for metabolite hydroxypioglitazone

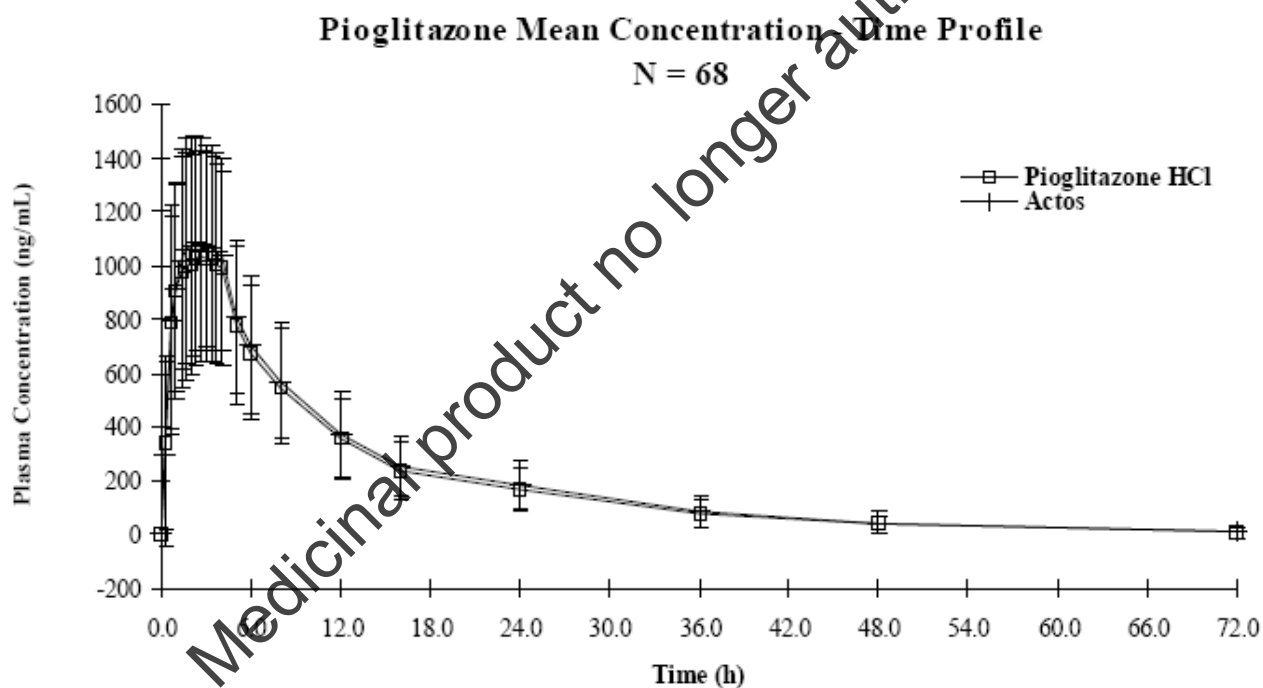
Pioglitazone HCl (A) vs Actos (B)

	AUC _{0-t}	AUC _{0-inf}	C _{max}
Ratio ¹	92.87%	92.68%	93.24%
90 % Geometric C.I. ²	87.68 % to 98.37 %	87.55 % to 98.12 %	86.54 % to 100.45 %
Intra-Subject CV	20.31 %	20.13 %	26.50 %

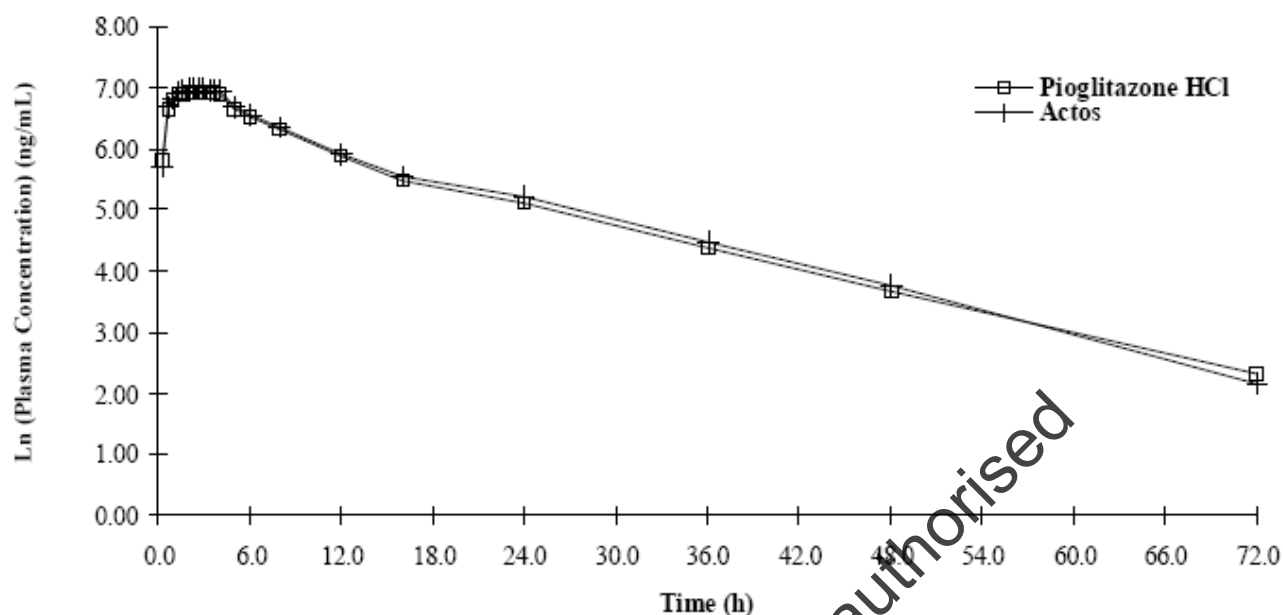
¹ Calculated using least-squares means according to the formula: $e^{(\text{Pioglitazone HCl (A)} - \text{Actos (B)})} \times 100$

² 90% Geometric Confidence Interval using ln-transformed data

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



Pioglitazone Ln (Mean Concentration) - Time Profile
N = 68



Safety data

A total of 29 treatment-emergent adverse events (TEAEs) were reported by 20 of the 72 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 10 TEAEs reported by 11.4% (n=8) of the 70 subjects who received Treatment A and 19 TEAEs reported by 20.0% (n=14) of the 70 subjects who received Treatment B. Although the total number of subjects experiencing adverse events was slightly higher following administration of Treatment B, adverse events were reported in low frequencies among subjects.

The most commonly reported TEAEs was "Headache" reported by 9.7% (n=7) of subjects who constituted the safety population.

The severity of each adverse event was graded according to the following categories: mild, moderate, or severe. Of the 29 TEAEs reported, 26 were graded as mild and 3 were graded as moderate.

No deaths, serious, or significant adverse events were reported during this study.

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.

2.4.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4 Post marketing experience

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

2.4.5 Discussion on Clinical aspects

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

2.4.6 Conclusions on clinical aspects

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

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant did not submit a risk management plan because this application concerns a generic for a reference medicinal product for which no safety concern requiring additional risk minimisation activities had been identified when the Marketing Authorisation application was submitted on 27 October 2010. However taking into account the outcome of the Article 20 procedure on already authorised pioglitazone containing products and the potential increased risk of bladder cancer, the MAH shall submit within one month of the Commission Decision a risk management plan which will incorporate risk minimisation measures, as detailed in the conditions or restrictions with regard to the safe and effective use of the medicinal product in Annex II, in line with those required for the reference medicinal product.

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

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

In addition, an updated RMP should be submitted:

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

- At the request of the European Medicines Agency

PSUR submission

The PSUR cycle for the product will follow the PSUR submission schedule of the reference medicinal product, which is on a 6 monthly cycle, having 1 February 2012 as its data lock point.

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 "as second or third line treatment of type 2 diabetes mellitus as described below,

as **monotherapy**

- in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance

as **dual oral therapy** in combination with

- metformin, in adult patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulphonylurea, only in adult patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea.

as **triple oral therapy** in combination with

- metformin and a sulphonylurea, in adult patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.

Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus adult patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

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

From a quality perspective, Sepioglin 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.

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

The test formulations of Sepioglin 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_f} , $AUC_{0-\infty}$, 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 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 Sepioglin is favourable as second or third line treatment of type 2 diabetes mellitus as described below:

as monotherapy in adult patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance;

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 CHMP 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

Pharmacovigilance System

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

Risk Management System

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

PSUR cycle

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).

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The MAH shall provide an educational pack targeting all physicians who are expected to prescribe/use Pioglitazone. Prior to distribution of the prescriber guide in each Member State, the MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority.

- This educational pack is aimed at strengthening awareness of important identified risks of bladder cancer and heart failure and the overall recommendations intended to optimise the benefit-risk margin at the patient level.

- The physician educational pack should contain: The Summary of Product Characteristics, package leaflet, and a Prescriber Guide.

The Prescriber Guide should highlight the following:

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

Divergent positions are appended to this report.

Medicinal product no longer authorised

Medicinal product no longer authorised

Appendix I

Divergent positions

Sepioglin (EMA/H/C/2324)

Divergent statement

We have a divergent opinion on the above mentioned Marketing Authorisation from that which has been adopted 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
Harald Enzmann (DE)	19 January 2012
Nela Vilceanu (RO)	19 January 2012