LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pioglitazone Rivopharm
(pioglitazone hydrochloride)

Asp no: 2018-0302, 2018-0303, 2018-0304

This module reflects the scientific discussion for the approval of Pioglitazone Rivopharm. The procedure was finalised on 2019-07-30. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Teva has submitted a National Marketing Authorisation Application in Sweden on behalf of the third party Rivopharm. This is following a divestment to third party commitment that Teva has entered with the European Commission (Case M. 7746) as a consequence of the acquisition of Allergan plc's generic pharmaceutical business in August 2016.
This National Application is a copy of the Centralised authorised procedure EMEA/H/C/2410 for Pioglitazone 15, 30 & 45 mg tablets.

The legal ground for Pioglitazone Rivopharm, 15 mg, 30 mg and 45 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Teva B.V. applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Glustin, 15 mg, 30 mg and 45 mg, tablet authorised in European Union since 2000, with Takeda Global Research and Development Centre (Europe) Ltd. as marketing authorisation holder.

The reference product used in the bioequivalence study is Actos, 45 mg, tablet from United Kingdom with Takeda Global Research and Development Centre (Europe) Ltd. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation is granted under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC.

The application was discussed in the CMDh, please see section VI for further information.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary. Reference is made to the assessment of centralised authorised procedure EMEA/H/C/2410 for Pioglitazone 15, 30 & 45 mg tablets.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Reference is made to the assessment of centralised authorised procedure EMEA/H/C/2410 for Pioglitazone 15, 30 & 45 mg tablets.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary. Reference is made to the assessment of centralised authorised procedure EMEA/H/C/2410 for Pioglitazone 15, 30 & 45 mg tablets.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pioglitazone Rivopharm (version 1.1 DLP 31 Oct 2018).

Safety specification

List of important risks and missing information	
Important identified risks	• Bladder cancer • Cardiac failure • Hepatic dysfunction • Peripheral oedema and weight gain • Bone fractures • Hypersensitivity reaction
Important potential risks	• Macular oedema • Malignancies other than bladder cancer • Cardiovascular ischaemic disease • Off-label use of pioglitazone as first-line therapy in T2DM
Missing information	• Use of pioglitazone in children

The safety specification is in line with the safety concerns listed in the RMP for Pioglitazone Teva Pharma (version 2.2 approved on 29 July 2014) assessed submitted within the renewal procedure EMEA/H/C/002410/R/0013 for Pioglitazone Teva Pharma.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measure
In line with the RMP for the for Pioglitazone Teva Pharma additional risk minimisation measure in form of educational material for HCPs (Prescriber‘s Guide) is proposed for the following risks:

- Bladder cancer
- Cardiac failure
- Off-label use of pioglitazone as first-line therapy in T2DM

Only routine risk minimisation is suggested for the remaining risks.
Overall, the proposed risk minimisation measures are endorsed.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Bladder cancer	Routine risk minimisation measures: SmPC sections 4.3, 4.8 and 5.3. PIL sections 2 and 4. SmPC section 4.4 where advice is given for promptly seeking the attention of physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment. Prescription only medicine. Additional risk minimisation measures:	Routine

	Educational Materials for Healthcare Professionals (HCPs): Prescriber's Guide	
Cardiac failure	Routine risk minimisation measures: SmPC sections 4.3, 4.8 and 5.1. PIL sections 2 and 4. SmPC section 4.4 where advice is given on monitoring signs and symptoms of heart failure, especially in patients with reduced cardiac reserve and those on insulin therapy. Prescription only medicine. Additional risk minimisation measures: Educational Materials for Healthcare Professionals (HCPs): Prescriber's Guide	Routine only
Hepatic dysfunction	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.8 and 5.2. SmPC section 4.4 where advice is given on monitoring the liver function. PIL section 4. PIL sections 2 and 3 where patients are advised of the requirement for blood tests before taking the drug and periodically during treatment to check liver function. Prescription only medicine. Additional risk minimisation measures: None	Routine only
Peripheral oedema and weight gain	Routine risk minimisation measures: SmPC sections 4.8 and 5.1. PIL sections 2 and 4. SmPC section 4.4. where advice is given on close monitoring of weight as well as monitoring signs and symptoms of weight gain and oedema, particularly in patients with reduced cardiac reserve and those on insulin therapy. PIL section 3 where advice is given on checking weight at regular intervals. Prescription only medicine. Additional risk minimisation measures: None	Routine only
Bone fractures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures: None	Routine only
Hypersensitivity reaction	Routine risk minimisation measures: SmPC sections 4.3 and 4.8. PIL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures: None	Routine only
Important potential risks		
Macular oedema	Routine risk minimisation measures: SmPC section 4.8. SmPC section 4.4 where advice is given for appropriate ophthalmological referral if patient reports disturbances in visual acuity. PIL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures: Not applicable.	Routine only

Malignancies other than bladder cancer	Routine risk minimisation measures: SmPC section 5.3. Prescription only medicine. Additional risk minimisation measures: Not applicable.	Routine only
Cardiovascular ischaemic disease	Routine risk minimisation measures: SmPC section 5.1. Prescription only medicine. Additional risk minimisation measures: Not applicable.	Routine only
Off-label use of pioglitazone as first-line therapy in T2DM	Routine risk minimisation measures: SmPC section 4.1 where advice is given for reviewing the patients after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). Prescription only medicine. Additional risk minimisation measures: Educational Materials for Healthcare Professionals (HCPs): Prescriber's Guide	Routine only
Missing information		
Use of pioglitazone in children	Routine risk minimisation measures: SmPC sections 4.2 and 5.1. PIL section 2. Prescription only medicine. Additional risk minimisation measures: Not applicable.	Routine only

Summary of the RMP
The submitted Risk Management Plan, version 1.1 with DLP 31 Oct 2018 is considered acceptable.

However, whenever the RMP for Pioglitazone Teva Pharma is updated relevant sections of the RMP for Pioglitazone Rivopharma should always also be up-dated accordingly.

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was English.
The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Pioglitazone Rivopharm is found adequate. There are no objections to approval of Pioglitazone Rivopharm, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

Additional risk minimisation measures are required in accordance to conditions under article 21a/22 of Directive 2001/83. See section VI.3

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

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)

VII. APPROVAL

Pioglitazone Rivopharm, 15 mg, 30 mg and 45 mg, tablet was approved in the national procedure on 2019-07-30.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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