

Public Assessment Report

Scientific discussion

Bicalutamide Accord 150 mg, film-coated tablets (bicalutamide)

NL/H/4485/001/DC

Date: 7 May 2020

This module reflects the scientific discussion for the approval of Bicalutamide Accord 150 mg, film-coated tablets. The procedure was finalised at 22 January 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.



List of abbreviations

ASMF Active Substance Master File

CEP Certificate of Suitability to the monographs of the European

Pharmacopoeia

CHMP Committee for Medicinal Products for Human Use

CMD(h) Coordination group for Mutual recognition and Decentralised

procedure for human medicinal products

CMS Concerned Member State
EDMF European Drug Master File

EDQM European Directorate for the Quality of Medicines

EEA European Economic Area

ERA Environmental Risk Assessment

ICH International Conference of Harmonisation

MAH Marketing Authorisation Holder

Ph.Eur. European Pharmacopoeia

PL Package Leaflet
RH Relative Humidity
RMP Risk Management Plan

SmPC Summary of Product Characteristics

TSE Transmissible Spongiform Encephalopathy



I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bicalutamide Accord 150 mg, film-coated tablets, from Accord Healthcare B.V.

The product is indicated either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression.

The product is also indicated for the management of patients with locally advanced, non-metastatic prostate cancer for whom surgical castration or other medical intervention is not considered appropriate or acceptable.

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

This decentralised procedure concerns a generic application claiming essential similarity with the European Reference Product Casodex 150 mg, film-coated tablets which has been registered in Austria by AstraZeneca Österreich GmbH since 21 November 2000 via a mutual recognition procedure (UK/H/0364/001, now AT/H/0905/001).

The concerned member states (CMS) involved in this procedure were Austria, Denmark, Estonia, Finland, Germany, Iceland, Italy, Lithuania, Latvia, Norway, Poland, Portugal, Romania, Spain, Sweden and Slovenia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bicalutamide Accord is a white to off-white, round, biconvex, film-coated tablet, debossed 'IO1' on one side and plain on the other side. Each tablet contains 150 mg bicalutamide.

The tablets are packed in clear PVC PVdC/Aluminium blisters.

The excipients are:

Tablet core - lactose monohydrate, sodium starch glycolate (maize), povidone and magnesium stearate

Film-coating - hypromellose 5 mPas (E464), titanium dioxide (E171) and macrogol (E1521)



II.2 Drug Substance

The active substance is bicalutamide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and practically insoluble in water. Different polymorphic forms of the active substance exist and the polymorphic form used for the drug product at issue is specified on the CEP and in the active substance specification.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP with additional tests for optical rotation, residual solvents, particle size and X-ray diffraction. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for four full-scaled batches stored at $25^{\circ}\text{C}/60\%$ RH (5 years data available) and $40^{\circ}\text{C}/75\%$ RH (6 months data) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. A bioequivalence study was performed with the 150 mg test product versus the Casodex 150 mg reference product. *In vitro* dissolution test were performed complementary to the bioequivalence study comparing the test product and reference product in four different media. The limit for dissolution has been set in line with



EMA/CHMP/ CVMP/QWP/336031/2017. Overall, the pharmaceutical development is considered acceptable.

Manufacturing process

The manufacturing process consists of sifting, granulation, blending, lubrication and compression and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients of the coating comply with in-house requirements and the other excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, disintegration time, loss on drying, dissolution, uniformity of dosage units, related substances, assay and microbiological examination. No test for polymorphic form is included in the drug product specification, since it has been demonstrated in the pharmaceutical development that the polymorphic form does not change during manufacture or storage of the drug product. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full-scaled batches stored at 25°C/60% RH (12 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 the commercial packaging. No significant changes were observed in long-term or accelerated conditions. Based on extrapolation the claimed shelf-life of 2 years can be accepted. This medicinal product does not require any special storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

<u>Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies</u>

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.



II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bicalutamide Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bicalutamide Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Casodex which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bicalutamide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Bicalutamide Accord 150 mg, film-coated tablets (Accord Healthcare B.V., NL) is compared with the pharmacokinetic profile of the reference product Casodex 150 mg, film-coated tablets (AstraZeneca Österreich GmbH, Austria).



The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product. The reference product used in the in the study has been sourced from the UK market and is the same product as the ERP from Austria.

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

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 58 healthy male subjects, aged 18-43 years. Each subject received a single dose (150 mg) of one of the 2 bicalutamide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 62 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3. 4, 5, 6, 8, 10, 12, 16, 20, 22, 24, 26, 28, 30 32, 34, 36, 42, 48, 60, 72, 96, 120, 168, 216, 288, 384 and 504 hours after administration of the products.

The design of the study is acceptable. A single dose study using 150 mg tablet is adequate to support the application for the proposed immediate-release product. The conduct of the study under fasting conditions is appropriate as the proposed products can be taken with or without food. Bioequivalence based on the R-bicalutamide enantiomer is agreed as the S-enantiomer is rapidly cleared relative to the predominant active R- enantiomer.

Analytical/statistical methods

The analytical method has been adequately validated and is 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

Two subjects discontinued on their own accord and two subjects were withdrawn due to medical grounds. Therefore, 52 completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of R-bicalutamide under fasted conditions.

Treatment	AUC _{0-t}	AUC _{0-∞}	C _{max}	t _{max}	
N=52	(ng.h/ml) (ng.h/ml)		(ng/ml)	(h)	
Test	322,254 ± 98,741	367,670 ± 111202	1,552 ± 411	28.00 (8.00– 72.00)	
Reference	361,859 ±	404,035 ±	1,711 ± 339	28.00	

	89,296	111,804		(4.00 – 60.02)
*Ratio	0.91	0.91	0.92	
(90% CI)	(0.87 – 0.94)	(0.87 – 0.95)	(0.89 – 0.96)	

 $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} area under the plasma concentration-time curve from time zero to thours

 $egin{array}{ll} C_{max} & maximum \ plasma \ concentration \\ t_{max} & time \ for \ maximum \ concentration \end{array}$

t_{1/2} half-life

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of S-bicalutamide under fasted conditions.

Treatment	AUC _{0-t}	AUC _{0-∞}	C _{max}	t _{max}	
N=52	(ng.h/ml) (ng.h/ml)		(ng/ml)	(h)	
Tost				4.00	
Test	2,659 ± 1,148	2859 ± 1132	103 ± 32	(1.00-36.00)	
Deference				3.99	
Reference	3,037 ± 1,271	3196 ± 1314	126 ± 37	(1.00-5.02)	
*Ratio	0.91	0.91	0.84		
(90% CI)	(0.86 – 0.97)	(0.86 – 0.97)	(0.80 - 0.89)		

 $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

 $egin{array}{ll} {C_{max}} & \mbox{maximum plasma concentration} \\ {t_{max}} & \mbox{time for maximum concentration} \\ \end{array}$

t_{1/2} half-life

Conclusion on bioequivalence study

The 90% confidence intervals of the R-bicalutamide enantiomer calculated for AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. For the S-enantiomer, the 90% CI Cmax ratio between the test and reference product is not within the acceptance range of 80.00-125.00%. This will not be raised as an issue as this is only supportive data. Based on the submitted bioequivalence study Bicalutamide Accord is considered bioequivalent with Casodex.

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).

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

^{*}In-transformed values

^{*}In-transformed values



interventions designed to identify, characterise, prevent or minimise risks relating to Bicalutamide Accord.

Table 3. Summary table of safety concerns as approved in RMP

	•		
Important identified risks	 Hypersensitivity reactions (including anaphylactic 		
	reactions)		
	 Hepatotoxicity (including hepatic failure) 		
	 Photosensitivity 		
	 Interstitual lung disease 		
	 Drug-interactions (co-administration with 		
	terfenadine, astemizole or cisapride)		
Important potential risks	 Cardiac disease (cardiac failure, myocardial infarction) 		
	 QT interval prolongation and Torsade de Pointes 		
	 Drug interactions 		
Missing information	None		

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Casodex. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Bicalutamide Fresenius Kabi 150 mg (UK/H/3982/001/DC). For bridging the design and lay-out the MAH made reference to (DK/H/2339/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.



VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bicalutamide Accord 150 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Casodex 150 mg, film-coated tablets. Casodex 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 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 Bicalutamide Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 January 2020.



STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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