CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bicalutamide 50 mg, film-coated tablets Sandoz B.V., the Netherlands

bicalutamide

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/739/001/DC
Registration number in the Netherlands: RVG 33515

25 June 2009

Pharmacotherapeutic group:	anti-androgens
ATC code:	L02BB03
Route of administration:	oral
Therapeutic indication:	advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration.
Prescription status:	prescription only
Date of authorisation in NL:	13 December 2007
Concerned Member States:	decentralised procedure with AT, DE, DK, ES, FI, FR, IE, IT, LU, PT.
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 Bicalutamide 50 mg film-coated tablets from Sandoz B.V., the Netherlands. The date of authorisation was on 13 December 2007 in the Netherlands. The product is indicated for treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration.

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

Bicalutamide is a non-steroidal antiandrogen, devoid of any other endocrine activity. It binds to androgen receptors without activating gene expression, and thus inhibits the androgen stimulus. Regression of prostatic tumours results from this inhibition. Clinically, discontinuation of bicalutamide can result in antiandrogen withdrawal syndrome in a subset of patients.
Bicalutamide is a racemate with its antiandrogenic activity being almost exclusively in the (R)-enantiomer.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Casodex® 50, 50 mg tablets which has been registered in the Netherlands by AstraZeneca B.V. since 25 July 1995 (original product, RVG 18356). In addition, reference is made to Casodex 50 authorisations in the individual member states (reference product).

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

This is considered acceptable for the following reasons:
- The application refers to a reference product which has been authorised under article 6 of Dir 2001/83/EC as amended for not less than 6/8 years in the EEA.
- The products have the same qualitative and quantitative composition in active substances as the reference product.
- The products have the same pharmaceutical form as the reference product.
- Bio-equivalence to the reference product has been demonstrated by appropriate bioavailability studies.

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 Casodex 50 mg, film-coated tablets, registered in Germany. 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.

No paediatric development programme has been submitted.

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
At the end of this procedure the active substance was not described in any pharmacopoeia. It is a white to almost white powder. The active substance is soluble in acetone and sparingly soluble in methanol. The active substance possesses a chiral carbon, and is a racemate. The substance shows polymorphism. The MAH uses the ASMF procedure.

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/EMEA 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.

Specification
In-house specifications are applied for the drug substance by both the MAH and the ASM. The specification is acceptable in view of the route of synthesis and the various European guidelines. For the drug substance only three potential impurities are identified. Data are provided regarding polymorphism, and zero optical rotation (confirming that the drug substance is a racemate). Batch analysis results are provided for 3 batches; batch results showed that the potentially genotoxic impurity was not detected.

Stability
Batches drug substance have been put on stability at 25°C/60% RH (36 months/3 batches; 24 months/2 batches; 18-9-3 months/each 1 batch) and 40°C/75% RH (6 months). The drug substance is packed in double transparent polythene bags in HDPE drums. A re-test period of 3 years (without specific storage condition) has been granted based on the provided stability data.

Medicinal Product

Composition
The product is an immediate-release, round, white, film-coated tablet containing 50 mg of the active substance biculatimide. The product is packaged in blisters composed of Alu-PVC/PVdC. The excipients and packaging are usual for this type of dosage form.

The excipients are:

Tablet core: Lactose monohydrate, Sodium starch glycolate type A, Povidone (E1201), Maize starch Magnesium stearate (E572).

Tablet coating: Methylcellulose, Titanium dioxide (E171), Triacetin (E1518).

The excipients comply with Ph. Eur. requirements were applicable, or with other relevant compendial requirements. These specifications are acceptable.

Pharmaceutical development
The development of the product has been described, the choice of excipients has been justified and their functions explained.

Information and data are provided demonstrating that the drug substance incorporated in the finished product will remain the same polymorph and same racemate after manufacturing and during shelf life (12 months at 40°C/75% RH). Additional data is provided demonstrating that the proposed dissolution method has sufficient "discriminating" ability. With this dissolution method the test- and reference bio-batches used in the bio-equivalence study have been tested, as well as numerous originator products from intended CMS markets. The comparing dissolution results are considered to be satisfactory.
All other aspects of the development of the drug product are satisfactorily performed and explained

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation has been performed on 3 batches, using granulate quantities representative for full scale batches and using granulate aliquots for the post-granulate stages.

The product specification includes tests on appearance, identity of active substance, identity of titanium dioxide, assay, related substances (degradation products), uniformity of dosage units Ph. Eur. 2.9.40 (release), dissolution, hardness, and microbial contamination. For the medicinal product the same potentially genotoxic impurity is limited to NMT 30 ppm. The analytical methods have been adequately described and validated.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of 3 batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH, in accordance with applicable European guidelines demonstrating the stability of the product over 6 months. On basis of the data submitted, a shelf life was granted of 1 year when stored under 25ºC. The restriction of the storage condition is justified due to out-of-spec results on dissolution (below 70% after 45 min). The labelled storage conditions are *"Do not store above 25° C"*.
After the finalisation of the MRP, the shelf life has been changed from 1 year to 2 years by a type IB variation NL/H/0738/001/IB/002 (see 'Steps taken after the finalisation of the initial procedure').

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose monohydrate, being from bovine origin, statements have been provided sufficiently ensuring that lactose is obtained from milk that is sourced from healthy animals in the same condition as milk for human consumption and that it complies with the concerning statements and guidelines regarding TSE safety of lactose monohydrate. There are no other substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

The non-clinical overview has adequately described the pre-clinical pharmacology, pharmacokinetics and toxicology of bicalutamide. Bicalutamide is a well-known active substance. No further studies are required.

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 bicalutamide 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

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Bicalutamide 50 mg is compared with the pharmacokinetic profile of the German reference product Casodex 50 mg.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

A single-centre, open label, single-dose, randomized, 1 period parallel study was carried out under fasting conditions in 50 healthy, non-smoking male subjects, aged 20-55 years. Each subject received a single dose (50 mg) of one of the 2 bicalutamide formulations. The tablet was orally administered with 240 ml water after a 10 hour fast. Blood samples were collected in EDTA blood tubes prior to study drug administration and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10, 12, 16, 24, 36, 48, 72, 96, 168, 336, 504, and 672 hours post-dose. Plasma samples were stored at -20°C until analysis for bicalutamide.
All 50 individuals completed the treatment. Data from all volunteers were included in the pharmacokinetic and statistical analysis, with the exception of one subject. For this subject treated with the reference product, the AUC_{0-t} was identified as imprecise due to missing of three consecutive blood samples in the terminal phase of the concentration time curve. The exclusion of this subject is acceptable taking into account the long halflife of the active substance..

Table 1. Pharmacokinetic parameters for bicalutamide (non-transformed values; as arithmetic mean ± SD, t_{max} as median, (range)) N=25 for test, N=24 for reference.

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test (N=25)	162263 ± 38222	165924 ± 39384	833 ± 101	24 (4.0-72)	105 ± 21
Reference (N=24)	155128 ± 33401	159899 ± 35568	784 ± 119	30 (3.0-7.2)	111 ± 28
***Ratio (90% CI)**	1.04 (0.91-1.20)	1.04 (0.90-1.19)	1.06 (0.98-1.15)	-	-
ANOVA CV (%)	24.3	24.4	13.6	-	-

$AUC_{0-\infty}$ 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
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Bicalutamide can be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of Bicalutamide. 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.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} 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 bicalutamide under fasted conditions, it can be concluded that Bicalutamide 50 mg film-coated tablets and the reference Casodex 50 mg film coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

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

Bicalutamide was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of bicalutamide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Casodex 50 mg film-coated tablets marketed by Astrazeneca B.V. The SPC has been adapted by a post-approval type II variation (NL/H/0739/001/II/004, see Annex to the PAR)).

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 10 participants, followed by two rounds with 10 participants each. The MAH's acceptance criteria for identification of suitable patients ensured that the sample was reflective of populations who are likely to rely on the leaflet. The age range of participants and mix of social grades was satisfactory. The questions covered all sections of the PIL and did not follow the layout of the PIL. The questionnaire is considered acceptable to test participant's ability to identify and understand the information provided in the PIL. In addition, participnats were also given an opportunity to make general comments on use of the PIL and its readability.

The results demonstrate that subjects representative of the target group for this product are able to identify and comprehend the information contained in the PIL. Ninety percent of participants were able to find the information requested in the PIL, of whom 90% can show that they understand it. The results are considered supportive of the proposed PIL. Revisions made to the PIL did not affect consistency with the SmPC. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bicalutamide 50 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Casodex 50 tablets. Casodex 50 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Casodex 50.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other bicalutamide containing products.

The board followed the advice of the assessors. From a clinical point of view this application was initially considered approvable by the RMS and all CMS's except one member state. This MS was of the opinion that based on the review of the data on quality, safety and efficacy, the application for Bicalutamide 50 mg in the treatment of patients with advanced prostate cancer, where a maximal androgen blockade (MAB) needs to be administered in conjunction with measures to suppress plasma testosterone to castration levels was not approvable unless the indication for Bicalutamide 50 mg should be restricted in duration to the following: *"Treatment of patients with advanced prostate cancer, where a maximal androgen blockade (MAB) needs to be administered in conjunction with measures to suppress plasma testosterone to castration levels during maximum four weeks following castration."*. In the view of this MS this is supported by a meta-analysis of maximal androgen blockade (MAB) trials concluded that there is no survival advantage of MAB over castration alone(cfr L. Collette, U.E. Studer, F.H. Schröder, L. Denis and R. Sylvester). Why trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. The Prostate 2001; 48(1): 29-39, Copyright © 2001 Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Since this issue was already referred to the CMD(h) for discussion as a result of a parallel MRP procedure (CZ/H/0133/01/MR). In this procedure RMS and CMS concluded in the CMD(h) meeting of April 2007 that the benefit-risk ratio for the identification of this generic product is identical to that of the originator.

All member states agreed to approve the applications with these post-approval commitments. The decentralised procedure was finished on 15 February 2007. Bicalutamide 50 mg film-coated tablets was authorised in the Netherlands on 13 December 2007.

The first PSUR will cover the period from December 2007 until February 2011. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 October 2011.

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_{max}	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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name of the medicinal product.	NL/H/0739/ 001/IB/001	IB	31-10-2007	7-12-2007	Approval	N
Change in the shelf-life of the finished product as packaged for sale from 1 year to 2 years.	NL/H/0739/ 001/IB/002	IB	18-10-2007	17-11-2007	Approval	N
Change in the name of the medicinal product in Poland.	NL/H/0739/ 001/IB/003	IB	5-12-2007	4-1-2008	Approval	N
Update SPC and PIL.	NL/H/0739/ 001/II/004	II	12-2-2009	13-4-2009	Approval	Y, Annex I

Annex I to the PAR

Variation assessment report for NL/H/0739/001/II/004

I. RECOMMENDATION

Based on the review of the data on quality the member states consider that the variation application NL/H/0739/001/II/004 for Bicalutamide 50 mg, filmcoated tablets, in the treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration (50mg) and in treatment either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression (3x50mg) for the following proposed changes:

Update of SPC and PIL following the publication of two documents.
- Referral opinion pursuant to Article 31 of Council Directive 2001/83/EC, as amended for bicalutamide 150 mg-containing medicinal products, dated 16 August 2007 (EMEA/378451/2007)
- European Core Safety Profile (CSP), dated 14 October 2008 (DK/H/PSUR/0006/001).

is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

Update of SPC and PL following the publication of two documents.
- Referral opinion pursuant to Article 31 of Council Directive 2001/83/EC, as amended for bicalutamide 150 mg-containing medicinal products, dated 16 August 2007 (EMEA/378451/2007)
- European Core Safety Profile (CSP), dated 14 October 2008 (DK/H/PSUR/0006/001).

III. SCIENTIFIC DISCUSSION

III.1 Product Information

This type II variation is with respect to the addition of a new indication.
Following the positive opinion for bicalutamide 150 mg to be used 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 information of the German reference product Casodex 50 mg was extended with the same indication. Based on this product, also a MRP for Bicalutamide EG 50 mg (FR/H/0330/001/MR, day 90: 14 February 2008) was recently approved for this extended indication. The product is registered in Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Sweden.
Therefore, the MAH suggests to add the information regarding treatment of locally advanced prostate cancer also to the product information of Bicalutamide 50 mg.
The proposed SPC was in sections 4.3 – 4.9 literally adapted to the European CSP. The additional information of section 4.1, 5.1, and 5.2 reflects the referral opinion on bicalutamide 150 mg (EMEA/378451/2007) and the current status of the procedure AT/H/0199-0201/001/DC (Bicalutamide Sandoz 150 mg).

Benefit-risk
To our opinion, as 3x50 mg and 150 mg tablet formulations are registered in Europe, the use of three tablets of the 50 mg formulation to obtain a 150 mg dose is acceptable without a bioequivalence study with a 150 mg reference product registered in the EU.

IV. OVERALL CONCLUSION

In the opinion of the member states there are no objections against this variation.