PUBLIC ASSESSMENT REPORT
Scientific Discussion

Bicalutamide EG 50mg, film-coated tablet
Bicalutamide

FR/H/330/01/ MR

Applicant: EG Labo

Date of the PAR: Novembre 2009
1. INTRODUCTION

This dossier concerned an abridged application pursuant to Article 10.1 of Directive 2001/83/EC as amended, for a medicinal product referring to Bicalutamide EG 50 mg, a so-called reference medicinal product with a Marketing authorisation granted in a Member State. This concerned product, Bicalutamide EG 50 mg, was considered essentially similar to Casodex 50 mg (bicalutamide), powder for solution for infusion, (Astra-Zeneca), as marketed in France. The branded product was first authorised for use in France the 5th of April 1995.

The approved indications were the following:

**Advanced prostate cancer**

*Treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration (daily dose 50 mg bicalutamide).*

**Locally advanced prostate cancer**

*Bicalutamide (daily dose 150 mg) is indicated either alone or as adjuvant therapy to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression (see section 5.1).*

1.1 About the product

Bicalutamide is a non steroidal anti-androgen without any other endocrine activity. The drug is used in combination therapy with either a LHRH analogue or surgical castration in the treatment of advanced prostate cancer, when hormonal therapy is indicated. This corresponds to the point where the disease has either become metastatic or spread locally, or both, and is therefore essentially incurable. The hormonal therapy options for advanced prostate cancer fall into two categories: monotherapy with either castration or anti-androgen, and combination therapy of castration with an anti-androgen in order to provide maximal androgen blockade (MAB).

Bicalutamide competitively inhibits the action of androgen by binding to cytosolic androgen receptors. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counters the effect of androgen and/or removes the source of androgen. This inhibition results in regression of prostatic tumour.
1.2 About the disease

Cancer of the prostate is the most common malignancy in men in the Western states and the third most common cause of cancer death in men above age 55 (after carcinomas of the lung and colon). The incidence and prevalence of prostate cancer has increased considerably over the past two decades. Although it is widely acknowledged that early detection is an important means of improving survival, at the time of diagnosis, in most countries, the majority of patients with prostate cancer present with locally advanced or metastatic disease.

Because growth of the normal prostate is dependent on testicular androgens, it was logical to examine androgen deprivation for treatment of advanced prostatic cancer. Androgen deprivation can be achieved by inhibition of the binding of androgen to its receptor protein (bicalutamide, cyproterone, or flutamide); inhibition of androgen synthesis by the testes and adrenals (aminogluthethimide); inhibition of pituitary gonadotropin and/or ACTH production (estrogen therapy, treatment with LHRH analogues (leuprolide or buserelin), or hypophysectomy; and surgical extirpation of the glands that synthesize androgens (castration and adrenalectomy).

2. QUALITY ASPECTS

2.1 Introduction

Bicalutamide EG 50 mg is presented as white, round biconvex film tablet. It contains 50 mg of bicalutamide as drug substance and lactose monohydrate, povidone, sodium starch glycolate, magnesium stearate and Opadry White Y-1-7000 (which contains hypromellose, titanium dioxide, macrogol 400) as excipients.

Bicalutamide EG 50mg film-coated tablet is packed in PVC/Aluminium or in PVC/PVDC-Aluminium blister.

2.2 Drug substance

Bicalutamide (INN) is a non-pharmacopoeial substance. It is a white to off-white, odourless crystalline powder which is practically insoluble in water.

The Active Substance Master File Procedure (Drug Master File (DMF)) is applied for this drug substance. The information provided in the restricted and open parts of the DMF is sufficient to support the application for the drug product.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

2.3 Medicinal product

Bicalutamide EG 50mg film-coated tablets is formulated using excipients described in the current European Pharmacopoeia.

All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The development is sufficiently described in accordance with the relevant European guidelines.
The objective of the pharmaceutical development was to obtain a tablet of 50mg bicalutamide essentially similar, i.e. containing an identical amount of drug substance, and being bioequivalent to the brand leader marketed by Astra Zeneca Casodex 50mg film-coated tablet. Comparative in vitro dissolution profiles and impurities profiles of the generic product and the reference product support the essentially similar character.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 3 years with no special storage precautions for each packaging.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

According to the article 10 of the directive 2001/83/EC amended by directive 2004/27/EC, and by way of derogation from article 8(i) of this directive, no preclinical tests are required to support a Marketing Authorization. The provided dossier was therefore based on the analysis of up-to-date available non clinical data published in the literature.

4. CLINICAL ASPECTS

4.1 Introduction

Bicalutamide is a non steroidal anti-androgen without any other endocrine activity. The drug is used in combination therapy with either a LHRH analogue or surgical castration in the treatment of advanced prostate cancer, when hormonal therapy is indicated.

4.2 Discussion on the clinical aspects

This Application is an abridged application and includes no specific studies in patients relating to the use of this product. Clinical experience is based on a review of the medicinal literature concerning the use of oxaliplatin. No new clinical studies were therefore provided but a retrospective analysis of the literature was carried out. Already published clinical studies and review were compiled and summarised by the Applicant.

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. A detailed Risk management Plan was not necessary for this product.

4.3 Pharmacokinetics

In support of the present application, one bioequivalence study conducted with the 50 mg strength tablet (STUDY CODE 40159) was submitted.
This study was conducted at Anapharm, Canada and was designed according to a standard, two-treatment, two-period, two-sequence, single-dose, crossover study under fasting conditions with a wash out period of 42 days between administrations.

30 healthy volunteers were randomised and enrolled into the study. All the volunteers enrolled completed the entire phases of the study and thus analysed.

In this study the generic tablet originated from a representative biobatch of the product to be in the market and the reference product is the brand leader in France CASODEX 50 mg.

The plasma concentrations of bicalutamide were monitored over a 672 h after drug administration.

Both test and reference in this study were administered as a racemate (R- and S-BICALUTAMIDE).

As no significant deviation from linearity may occur with bicalutamide enantiomers when doses ranging from 10 up to 50 mg and as no vivo inter-conversions is known for bicalutamide enantiomers from the racemate mixture the use of a non stereoselective analytical technique was acceptable and samples in this study were assayed for bicalutamide by the means of a non chiral validated LC-MS technique.

The primary pharmacokinetic parameters assessed were AUC0-t, AUC0-inf, Cmax and Tmax

The statistical analysis of the data was conducted according to up to date methods.

The analysis consists in ANOVA analysis and the estimation of 90% Confidence interval of the ratios test/reference for each PK parameter of interest.

The main results are tabulated below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t hr.ng/ml (S.D.)</th>
<th>AUC0-∞ hr.ng/ml (S.D)</th>
<th>Cmax ng/ml (S.D)</th>
<th>tmax h (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (S.D.)</td>
<td>143278 (28103)</td>
<td>148820 (30695)</td>
<td>693 (99.7)</td>
<td>24 (3-48)</td>
</tr>
<tr>
<td>Reference (S.D.)</td>
<td>148760 (32639)</td>
<td>154127 (36776)</td>
<td>707.9 (91.3)</td>
<td>36 (3-48)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>[93;102]% 97%</td>
<td>[93;102]% 97.4%</td>
<td>[96;101]% 98.1</td>
<td></td>
</tr>
<tr>
<td>Point estimate</td>
<td></td>
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*Intra-subject CV (%) | 9.23% | 11.4% | 15.6%

*log-transformed values

Conclusion:
The bioequivalence of bicalutamide tablet to respective reference the French brand leader was clearly demonstrated.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The reference product is marketed in France since 1995. The innovator (Casodex®, Astra Zeneca) is also marketed in most European countries. The chemical-pharmaceutical quality of Bicalutamide EG 50mg film-coated tablet was demonstrated. Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC was also consistent with that of the reference product. Since the medical benefits to be expected from this formulation are similar to those of existing and already marketed formulation, the RMS recommended to approve this Application. Therefore, the Member States mutually recognised the French evaluation of the marketing authorisation and there was no discussion in the CMD(h).