BICALUTAMIDE 50MG FILM-COATED TABLETS
BICALUTAMIDE 150MG FILM-COATED TABLETS

UKPAR

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BICALUTAMIDE 50MG FILM-COATED TABLETS
BICALUTAMIDE 150MG FILM-COATED TABLETS

LAY SUMMARY

On 21st April 2009, the MHRA granted Kiron Pharmaceutica BV Marketing Authorisations (licences) for the medicinal products Bicalutamide 50 and 150mg Film-Coated Tablets (PL 22983/0001-2). These are prescription only medicines (POM) for the treatment of advanced prostate carcinoma.

Bicalutamide 50 and 150mg Film-Coated Tablets contain the active ingredient bicalutamide, which belongs to a group of medicines known as non-steroidal antiandrogens. These block the undesired effects of the male sex hormone (androgens) and inhibit cell growth in the prostate.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Bicalutamide 50 and 150mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Bicalutamide 50 and 150mg Film-Coated Tablets to Kiron Pharmaceutica BV (PL 22983/0001-2) on 21st April 2009. The products are prescription-only medicines.

These are national abridged applications for Bicalutamide 50 and 150mg Film-Coated Tablets claiming essential similarity to the originator product, Casodex 50mg and 150mg Tablets, first licensed to Zeneca Limited on 23rd February 1995 and 17th June 1999, respectively. Following a change of ownership, the marketing authorisation holder for Casodex 50 and 150mg Tablets is now AstraZeneca UK Limited.

The products contain the active ingredient bicalutamide and are indicated for the:

- Treatment of advanced prostate cancer in combination with luteinizing hormone-releasing hormone (LHRH) analogue therapy or surgical castration (50mg only)
- Either alone or as adjuvant to radical prostatectomy or radiotherapy in patients with locally advanced prostate cancer at high risk for disease progression (150mg only)

Bicalutamide is a non-steroidal antiandrogen, which binds to androgen receptors in the prostate without activating gene expression and prevents the physiological effects of dihydrotestosterone, thus inhibiting androgen stimulus. The drug is optically active chiral drug whose antiandrogenic activity resides almost exclusively in the (R)-enantiomer.
PHARMACEUTICAL ASSESSMENT

Active Substance

INN: Bicalutamide
Chemical Name: RS N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl propanamide
Molecular Formula: C_{18}H_{14}F_{4}N_{2}O_{4}S
Chemical Structure:

![Chemical Structure Image]

Molecular Weight: 430.38
Appearance: White to almost-white crystalline powder
Properties: Soluble in DMF and acetone, slightly soluble in methanol, practically insoluble in chloroform and water.
Chirality: The RS Bicalutamide is a racemic anti androgen. A mixture of R and S enantiomers are generally referred to as a racemic mixture. R enantiomer is primarily responsible for the anti-androgenic activity.
Polymorphism: Bicalutamide exists in two forms i.e. crystalline form-1 and crystalline form-2.

There is no European Pharmacopoeia monograph for bicalutamide.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance bicalutamide. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting the proposed retest period when stored in the approved containers.
Other Ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, povidone K-29/32, crospovidone, sodium laurilsulfate, magnesium stearate, hypromellose, titanium dioxide and Macrogol 4,000.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

Lactose monohydrate is the only ingredient that comes from an animal or human source. It has been confirmed that the lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce products with 50mg and 150mg bicalutamide that are tolerable and can be considered as generic products to the originator products Casodex 50mg and 150mg Tablets (AstraZeneca UK Limited).

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative in vitro dissolution and impurity profiles have been generated for the proposed and originator products with satisfactory results.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products along with an appropriate account of the manufacturing process. The manufacturing process has shown satisfactory results on validation batches.

Suitable commitments have been provided to perform validation on the first three commercial-scale batches as soon as these become available.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
All strengths of tablet are packaged in aluminium/polyvinylchloride/polyvinylidene chloride/polyethylene blister strips, which are packed into cardboard cartons in pack sizes of 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 98, 100, 140, 200 or 280 tablets.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations regarding materials for use in contact with food.

The marketing authorisation holder has confirmed that not all pack sizes are intended for marketing and has committed to submitted mock-ups for any pack size to the MHRA before marketing any pack size.

**Stability of the product**
Stability studies were performed on batches of all strengths of finished product in accordance with current guidelines. The results support a shelf-life of 3 years for both strengths, with no specific storage conditions.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product (see Clinical Assessment).

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics**
These are consistent with those for the reference products and are satisfactory.

**Labelling**
These are satisfactory

**Patient Information Leaflet**
This is consistent with that for the reference products and is satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Forms**
These are satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been provided for the proposed and reference products.
PRECLINICAL ASSESSMENT

These applications are generic medicinal products of Casodex 50 and 150mg Tablets (AstraZeneca UK Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the application, bioequivalence studies for the 50 mg and 150 mg film-coated tablets have been submitted.

Efficacy Studies
No new efficacy data have been submitted and none are required for this generic application.

Bioequivalence Study (50mg): a single-centre, randomized, single-dose, open-label, crossover study, comparing the pharmacokinetic profiles of Bicalutamide 50 mg Film-Coated Tablets (Test) versus Casodex 50 mg Film-Coated Tablets (Reference - AstraZeneca, UK) in healthy male subjects under fasted conditions.

Blood samples for pharmacokinetic analysis were taken pre- and up to 648 hours post dose. The log-transformed results for both enantiomers of active substance are presented below:

<table>
<thead>
<tr>
<th></th>
<th>Geometric means</th>
<th>Ratio T/R</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>%</td>
</tr>
<tr>
<td>AUC((0-t))</td>
<td>171015.3</td>
<td>183058.5</td>
<td>93.42</td>
</tr>
<tr>
<td>AUC((0-\alpha))</td>
<td>177175.5</td>
<td>190450.1</td>
<td>93.03</td>
</tr>
<tr>
<td>C(_{max})</td>
<td>901.1</td>
<td>954.7</td>
<td>94.39</td>
</tr>
<tr>
<td>C(_{max}/AUC((0-\alpha))</td>
<td>0.0051</td>
<td>0.0050</td>
<td>101.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Geometric means</th>
<th>Ratio T/R</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>%</td>
</tr>
<tr>
<td>AUC((0-t))</td>
<td>1701.64</td>
<td>1830.47</td>
<td>92.96</td>
</tr>
<tr>
<td>AUC((0-\alpha))</td>
<td>1756.67</td>
<td>1892.16</td>
<td>92.84</td>
</tr>
<tr>
<td>C(_{max})</td>
<td>58.34</td>
<td>61.91</td>
<td>94.23</td>
</tr>
<tr>
<td>C(_{max}/AUC((0-\alpha))</td>
<td>0.033</td>
<td>0.033</td>
<td>101.50</td>
</tr>
</tbody>
</table>

For both enantiomers, the 90% confidence intervals lie between the acceptance criteria stated in the *Notes for Guidance on Investigation of Bioavailability and Bioequivalence*. Thus, bioequivalence has been shown between the test and reference products.
Bioequivalence Study (150mg): a single-centre, randomized, single-dose, open-label, crossover study, comparing the pharmacokinetic profiles of Bicalutamide 150mg Film-Coated Tablets (Test) versus Casodex 150mg Film-Coated Tablets (Reference - AstraZeneca, UK) in healthy male subjects under fasted conditions.

Blood samples for pharmacokinetic analysis were taken pre- and up to 648 hours post dose. The log-transformed results for both enantiomers of active substance are presented below:

### R-bicalutamide:

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>Reference</th>
<th>Ratio T/R</th>
<th>90% CI Lower</th>
<th>90% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{0-t}) ng.h/ml</td>
<td>345455.3</td>
<td>327844.9</td>
<td>105.37</td>
<td>96.08</td>
<td>115.56</td>
</tr>
<tr>
<td>AUC(_{0-\alpha}) ng.h/ml</td>
<td>355347.8</td>
<td>339225.6</td>
<td>104.75</td>
<td>94.92</td>
<td>115.61</td>
</tr>
<tr>
<td>C(_{\text{max}}) ng/ml</td>
<td>1748.0</td>
<td>1625.7</td>
<td>107.52</td>
<td>100.69</td>
<td>114.82</td>
</tr>
<tr>
<td>C(<em>{\text{max}}/\text{AUC}</em>{0-\alpha}) h(^{-1})</td>
<td>0.0049</td>
<td>0.0048</td>
<td>102.64</td>
<td>94.45</td>
<td>111.56</td>
</tr>
</tbody>
</table>

### S-bicalutamide:

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>Reference</th>
<th>Ratio T/R</th>
<th>90% CI Lower</th>
<th>90% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{0-t}) ng.h/ml</td>
<td>3645.22</td>
<td>3333.52</td>
<td>109.35</td>
<td>98.74</td>
<td>121.10</td>
</tr>
<tr>
<td>AUC(_{0-\alpha}) ng.h/ml</td>
<td>3716.36</td>
<td>3427.30</td>
<td>108.43</td>
<td>97.75</td>
<td>120.28</td>
</tr>
<tr>
<td>C(_{\text{max}}) ng/ml</td>
<td>106.94</td>
<td>93.42</td>
<td>114.47</td>
<td>103.17</td>
<td>127.01</td>
</tr>
<tr>
<td>C(<em>{\text{max}}/\text{AUC}</em>{0-\alpha}) h(^{-1})</td>
<td>0.029</td>
<td>0.027</td>
<td>105.57</td>
<td>92.68</td>
<td>120.25</td>
</tr>
</tbody>
</table>

For both enantiomers, the 90% confidence intervals lie between the acceptance criteria stated in the *Notes for Guidance on Investigation of Bioavailability and Bioequivalence*. Thus, bioequivalence has been shown between the test and reference products.

**Efficacy**

No new data have been provided.

**Safety**

No new data have been provided.

**Expert Reports**

A clinical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**

These are consistent with those for the reference products and are satisfactory.

**Patient Information Leaflets (PIL)**

These are consistent with the SPC and are satisfactory.
LABELLING
These are satisfactory

APPLICATION FORMS (MAA)
These are satisfactory.

DISCUSSION
Bioequivalence has been satisfactorily demonstrated for the 50mg and 150mg product, in accordance with CHMP criteria.

MEDICAL CONCLUSION
The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Bicalutamide 50 and 150mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s 50mg and 150mg strength tablets and their respective reference products (Casodex 50mg and 150mg Tablets, AstraZeneca UK Limited).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products, where necessary.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with bicalutamide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
BICALUTAMIDE 50MG FILM-COATED TABLETS  
BICALUTAMIDE 150MG FILM-COATED TABLETS

**STEPS TAKEN FOR ASSESMENT**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 9th March 2005</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 23rd March 2005</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 24th November 2005, 9th January 2006, 30th October 2006, 14th October 2008, and related to the clinical dossiers on 9th January 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 9th January 2006, 20th September 2006, 8th March 2007 and 23rd February 2009 for the quality sections, and 7th February 2006 for the clinical sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 21st April 2009</td>
</tr>
</tbody>
</table>
## BICALUTAMIDE 50MG FILM-COATED TABLETS
BICALUTAMIDE 150MG FILM-COATED TABLETS

### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
Bicalutamide 50 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of bicalutamide
Excipient: each tablet contains 60.44 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White, round, biconvex film-coated tablet debossed with BCM 50 on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of advanced prostate cancer in combination with luteinising hormone-releasing hormone (LHRH) analogue therapy or surgical castration.

4.2 Posology and method of administration
Adult males, including elderly patients: the dosage is one 50 mg tablet to be taken orally once a day.

Children and adolescents:
Bicalutamide is not indicated in children or adolescents.

The tablets should be swallowed whole with liquid.

Treatment with bicalutamide should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Renal impairment
No dose adjustment is necessary in patients with renal impairment. There is no experience with the use of bicalutamide in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. The medicinal product may accumulate in patients with moderate to severe hepatic impairment (see section 4.4)

4.3 Contraindications
Bicalutamide is contraindicated in females and children.

Bicalutamide must not be given to any patient who has shown a hypersensitivity reaction to its use.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use
Initiation of treatment should be under the direct supervision of a specialist.

Bicalutamide is extensively metabolised in the liver. Data suggests that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of changes are expected to occur within the first 6 months of bicalutamide therapy.
Severe hepatic changes and hepatic failure have been observed rarely with bicalutamide (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycaemic control in those with pre-existing diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving bicalutamide in combination with LHRH agonists.

Bicalutamide has been shown to inhibit Cytochrome P450 (CYP 3A4), as such caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4, (see sections 4.3 and 4.5).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between bicalutamide and LHRH analogues.

In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a drug interaction potential with bicalutamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of bicalutamide for 28 days. For drugs with a narrow therapeutic index such an increase could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated (see section 4.3) and caution should be exercised with the co-administration of bicalutamide with compounds such as ciclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporin, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of bicalutamide therapy.

Caution should be exercised when prescribing bicalutamide with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide which theoretically could lead to an increase in side effects.

In vitro studies have shown that bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding site. It is therefore recommended that if bicalutamide is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

4.6 Pregnancy and lactation

Bicalutamide is contraindicated in females and must not be given to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines

Bicalutamide is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.
4.8 Undesirable effects
In this section undesirable effects are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Table 1: frequency of adverse reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Bicalutamide 50mg (+ LHRH analogue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic</td>
<td>Common</td>
<td>Anaemia</td>
</tr>
<tr>
<td>system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system</td>
<td>Uncommon</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>(including angioneurotic oedema and urticaria)</td>
</tr>
<tr>
<td>Metabolism and</td>
<td>Common</td>
<td>Anorexia</td>
</tr>
<tr>
<td>nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Decreased libido, Depression</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Very common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very common</td>
<td>Hot flush</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Abdominal pain, Constipation, Nausea Dyspepsia, Flatulence</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Common</td>
<td>Hepatic changes (including elevated levels of transaminases, jaundice)/hepato-biliary disorders</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hepatic failureb</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Alopecia, Hirsuitism/ hair re-growth, Dry skin, Pruritis, Rash</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Very common</td>
<td>Gynaecomastia and breast tendernessc Impotence</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Asthenia, Chest pain, Oedema</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common</td>
<td>Weight gain</td>
</tr>
</tbody>
</table>

a Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
b Hepatic failure has occurred rarely in patients treated with bicalutamide, but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4)
c May be reduced by concomitant castration.
In addition, cardiac failure was reported in clinical trials (as a possible adverse drug reaction in the opinion of investigating clinicians, with a frequency of >1%) during treatment with bicalutamide plus an LHRH analogue. There is no evidence of a causal relationship with drug treatment.
4.9 Overdose
There is no human experience of over dosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since bicalutamide is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anti-androgens, ATC-code: L02 B B03

Bicalutamide is a non-steroid anti-androgen; it has no additional endocrine activity. It is bound to androgen receptors without activating gene expression and thereby inhibits androgen stimulation. The result of this inhibition is regression of prostate tumours. From the clinical point of view interruption of therapy in some patients could result in manifestation of the anti-androgen withdrawal syndrome.

Bicalutamide is a racemate with an anti-androgen effect, which is present almost exclusively in its R-enantiomer.

5.2 Pharmacokinetic properties
Bicalutamide is well absorbed after oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

S-enantiomer is rapidly cleared in comparison to the R-enantiomer, which half-life of plasma elimination is approximately 1 week.

With regular daily administration of bicalutamide the concentration of the R-enantiomer in plasma in comparison with S-enantiomer is approximately ten-fold, which is caused by its lengthy elimination half-life.

The plasma concentrations of R-enantiomer reach approximately 9 microgram/ml in the case of a daily dose of 50 mg of bicalutamide. From the total number of enantiomers present in plasma in the steady state there is 99% of R-enantiomer, which has a dominant share in the therapeutic effect.

Pharmacokinetics of R-enantiomer are not affected by age, renal impairment or mild to moderate hepatic impairment. It has been shown that in patients with severe liver impairment the R-enantiomer is eliminated slower from plasma.

Bicalutamide is highly protein bound (racemate 96%, R-Bicalutamide 99.6%) and is extensively metabolised (by oxidation and glucuronidation): its metabolites are eliminated via the kidneys and bile in approximately equal proportions. After excreting to bile, hydrolysis of glucuronides occurs. Metabolised bicalutamide is rarely present in urine.

5.3 Preclinical safety data
Bicalutamide is a pure and potent androgen receptor antagonist in experimental animals and humans. The main secondary pharmacological action is induction of CYP450 dependent mixed function oxidases in liver. Enzyme induction has not been observed in humans. Target organ changes in animals are clearly related to the primary and secondary pharmacological action of bicalutamide comprised of involution of androgen-dependent tissues; thyroid gland, hepatic and Leydig cell hyperplasias and neoplasias or cancer; disturbance of male offspring sexual differentiation; reversible impairment of fertility in males. Genotoxicity studies did not reveal any mutagenic potential of bicalutamide. All adverse effects observed in animal studies are considered to be species-specific, having no relevance for humans in the indicated clinical setting.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
lactose monohydrate
Povidone K-29/32
Crospovidone
Sodium laurilsulfate
Magnesium stearate
Coating:
Lactose monohydrate
Hypromellose
Titanium oxide (E 171)
Macrogol 4,000

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product requires no special conditions for storage.

6.5 Nature and contents of container
PVC/PE/PVDC/Al blister, box.

The packaging contains 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 98, 100 140, 200 or 280 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Kiron Pharmaceutica BV
Sterreschansweg 79
6522 GM Nijmegen
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 22983/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/04/2009

10 DATE OF REVISION OF THE TEXT
21/04/2009

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
1 NAME OF THE MEDICINAL PRODUCT
Bicalutamide 150 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 150 mg of bicalutamide
Excipients: each tablet contains 181 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White, round, biconvex film-coated tablet, debossed with BCM 150 on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Bicalutamide 150mg 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 (see section 5.1).

4.2 Posology and method of administration
Adult males, including elderly patients: 150 mg (1 tablet) once per day, always at the same time (usually in the morning or evening).

Children and adolescents:
Bicalutamide is not indicated in children or adolescents.

The tablets should be swallowed whole with liquid.

Minimum treatment duration is two years.

Renal impairment
No dose adjustment is necessary in patients with renal impairment. There is no experience with the use of bicalutamide in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4).

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. The medicinal product may accumulate in patients with moderate to severe hepatic impairment (see section 4.4.)

4.3 Contraindications
Bicalutamide is contraindicated in females and children.

Bicalutamide must not be given to any patient who has shown a hypersensitivity reaction to its use.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use
Initiation of treatment should be under the direct supervision of a specialist.

Bicalutamide is extensively metabolised in the liver. Data suggests that its elimination may be slower in subjects with severe hepatic impairment and this could lead to increased accumulation of bicalutamide. Therefore, bicalutamide should be used with caution in patients with moderate to severe hepatic impairment.

Periodic liver function testing should be considered due to the possibility of hepatic changes. The majority of changes are expected to occur within the first 6 months of bicalutamide therapy.
Severe hepatic changes and hepatic failure have been observed rarely with bicalutamide (see section 4.8). Bicalutamide therapy should be discontinued if changes are severe.

Bicalutamide has been shown to inhibit Cytochrome P450 (CYP 3A4), as such caution should be exercised when co-administered with drugs metabolised predominantly by CYP 3A4, (see sections 4.3 and 4.5).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
In vitro studies have shown that R-bicalutamide is an inhibitor of CYP 3A4, with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity.

Although clinical studies using antipyrine as a marker of cytochrome P450 (CYP) activity showed no evidence of a drug interaction potential with bicalutamide, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of bicalutamide for 28 days. For drugs with a narrow therapeutic index such an increase could be of relevance. As such, concomitant use of terfenadine, astemizole and cisapride is contraindicated (see section 4.3) and caution should be exercised with the co-administration of bicalutamide with compounds such as ciclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For ciclosporin, it is recommended that plasma concentrations and clinical condition are closely monitored following initiation or cessation of bicalutamide therapy.

Caution should be exercised when prescribing bicalutamide with other drugs which may inhibit drug oxidation e.g. cimetidine and ketoconazole. In theory, this could result in increased plasma concentrations of bicalutamide which theoretically could lead to an increase in side effects.

In vitro studies have shown that bicalutamide can displace the coumarin anticoagulant, warfarin, from its protein binding site. It is therefore recommended that if bicalutamide is started in patients who are already receiving coumarin anticoagulants, prothrombin time should be closely monitored.

4.6 Pregnancy and lactation
Bicalutamide is contraindicated in females and must not be given to pregnant women or nursing mothers.

4.7 Effects on ability to drive and use machines
Bicalutamide is unlikely to impair the ability of patients to drive or operate machinery. However, it should be noted that occasionally somnolence may occur. Any affected patients should exercise caution.

4.8 Undesirable effects
In this section undesirable effects are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Table 2: frequency of adverse reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Bicalutamide 150mg (monotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Common</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>Hypersensitivity reactions (including angioneurotic oedema and urticaria)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Anorexia</td>
</tr>
</tbody>
</table>
Psychiatric disorders  Common  Decreased libido, Depression

Nervous System Disorders  Common  Dizziness, Somnolence
Common  Somnolence

Vascular disorders  Common  Hot flush

Respiratory, thoracic and mediastinal disorders  Uncommon  Interstitial lung disease

Gastrointestinal disorders  Common  Abdominal pain, Constipation, Dyspepsia, Flatulence, Nausea
Common  Dyspepsia, Flatulence

Hepato-biliary disorders  Common  Hepatic changes (including elevated levels of transaminases, jaundice)/hepato-biliary disorders
Rare  Hepatic failure

Skin and subcutaneous tissue disorders  Very common  Rash

Common  Alopecia, Hirsuitism/hair re-growth, Dry skin, Pruritis

Renal and urinary disorders  Common  Haematuria

Reproductive system and breast disorders  Very common  Gynaecomastia and breast tenderness
Common  Impotence

General disorders and administration site conditions  Very common  Asthenia,

Common  Chest pain, Oedema

Investigations  Common  Weight gain

a Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy.
b Hepatic failure has occurred rarely in patients treated with bicalutamide, but a causal relationship has not been established with certainty. Periodic liver function testing should be considered (see also section 4.4)
c The majority of patients receiving bicalutamide 150 mg as monotherapy experience gynaecomastia and/or breast pain. In studies these symptoms were considered to be severe in up to 5% of the patients Gynaecomastia may not resolve spontaneously following cessation of therapy, particularly after prolonged treatment.

4.9 Overdose
There is no human experience of over dosage. There is no specific antidote; treatment should be symptomatic. Dialysis may not be helpful, since bicalutamide is highly protein bound and is not recovered unchanged in the urine. General supportive care, including frequent monitoring of vital signs, is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anti-androgens, ATC code: L02BB03

Bicalutamide is a non-steroidal anti-androgen without any other endocrine activity. It binds to androgen receptors without activating gene expression and thus inhibits androgen stimulation.

Inhibition results in the regression of prostatic tumours. Treatment discontinuation may result in antiandrogen withdrawal syndrome in some patients.
Bicalutamide is a racemate, the (R)-enantiomer of which has most of the anti-androgen activity.

Bicalutamide 150 mg was studied as a treatment for patients with localized (T1-T2, N0 or NX, M0) or locally advanced (T3-T4, any N, M0; T1-T2, N+, M0) non-metastatic prostate cancer, in a combined analysis of 3 placebo-controlled double-blind studies in 8,113 patients, where the product was given as immediate hormone therapy or as adjuvant to radical prostatectomy or radiotherapy (primarily external beam radiation). At 7.4 years median follow-up, 27.4 % of all bicalutamide-treated patients and 30.7 % of all placebo-treated patients had experienced objective disease progression.

A reduction in risk of objective disease progression was seen across most patient groups but was most evident in those at highest risk of disease progression. Therefore, clinicians may decide that the optimum medical strategy for a patient at low risk of disease progression, particularly in the adjuvant setting following radical prostatectomy, may be to defer hormonal therapy until signs that the disease is progressing.

No overall survival difference was seen at 7.4 years median follow-up with 22.9% mortality (HR = 0.99; 95% confidence interval 0.91 to 1.09). However some trends were apparent for patients in exploratory subgroup analyses.

Progression-free survival and overall survival data for patients with locally advanced disease are summarised in the following tables:

Table 3: Progression-free survival in locally advanced disease by therapy sub-group

<table>
<thead>
<tr>
<th>Analysis population</th>
<th>Events (%) in Bicalutamide patients</th>
<th>Events (%) in placebo patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>193/335 (57.6)</td>
<td>222/322 (68.9)</td>
<td>0.60 (0.49 to 0.73)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>66/161 (41.0)</td>
<td>86/144 (59.7)</td>
<td>0.56 (0.40 to 0.78)</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>179/870 (20.6)</td>
<td>213/849 (25.1)</td>
<td>0.75 (0.61 to 0.91)</td>
</tr>
</tbody>
</table>

Table 4: Overall survival in locally advanced disease by therapy sub-group

<table>
<thead>
<tr>
<th>Analysis population</th>
<th>Deaths (%) in Bicalutamide patients</th>
<th>Deaths (%) in placebo patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>164/335 (49.0)</td>
<td>183/322 (56.8)</td>
<td>0.81 (0.66 to 1.01)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>49/161 (30.4)</td>
<td>61/144 (42.4)</td>
<td>0.65 (0.44 to 0.95)</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>137/870 (15.7)</td>
<td>122/849 (14.4)</td>
<td>1.09 (0.85 to 1.39)</td>
</tr>
</tbody>
</table>

For patients with localised disease, receiving bicalutamide alone, there was no significant difference in progression free survival. In these patients there was also a trend toward decreased survival compared with placebo patients (HR=1.16, 95% CI 0.99 to 1.37). In view of this, the benefit-risk profile for the use of bicalutamide is not considered favourable in this group of patients.

The effectiveness of bicalutamide 150 mg in the treatment of patients with locally advanced prostatic carcinoma without metastases, for whom primary treatment with hormones was indicated, was evaluated separately using the meta-analysis of two studies comprising 480 patients with prostatic carcinoma without metastases (M0) who had not been treated before. There was no significant difference in survival (HR=1.05 (CI=0.81-1.36), p=0.669) or in the interval until progression (HR=1.20 (CI 0.96-1.51), p=0.107) between the group treated with bicalutamide 150 mg and the group treated with castration. A general trend with respect to quality of life in favour of bicalutamide 150 mg in comparison with castration was observed; the subgroups that provided these data showed significantly higher sexual appetite (p=0.029) and fitness (p=0.046).
Combined analysis of 2 clinical studies comprising 805 patients with metastatic prostatic carcinoma, who had not been treated before with expected mortality 43%, showed that the treatment with bicalutamide 150 mg is less effective than castration as for the survival time (HR = 1.30 [confidence interval 1.04 – 1.65]). The estimated difference is 42 days while the mean survival time is 2 years.

5.2 Pharmacokinetic properties
Bicalutamide is well absorbed after oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

The S-enantiomer is rapidly cleared in comparison to the R-enantiomer, which plasma elimination half-life is approximately 1 week.

With regular daily administration of bicalutamide, the concentration of the R-enantiomer in plasma compared to the S-enantiomer is approximately tenfold, which is caused by its lengthy elimination half-life.

With daily doses of 150 mg bicalutamide, equilibrium plasmatic concentrations of the R enantiomer reach approximately 22 micrograms/ml. From the total number of enantiomers present in plasma at equilibrium condition, 99% consists of the R-enantiomer, which has a dominant share in the therapeutic effect.

The pharmacokinetics of the R-enantiomer are not influenced by age, renal impairment or mild to moderate hepatic impairment. It has been proven that the R-enantiomer is eliminated more slowly from plasma in patients with severe hepatic impairment.

Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and is largely metabolised (by oxidation and glucuronidation): its metabolites are eliminated via the kidneys and bile in approximately equal proportions. The hydrolysis of glucuronides sets in after excretion into the bile. Metabolised bicalutamide is rarely present in urine.

In the sperm of males using bicalutamide 150 mg, an average concentration of 4.9 μg/ml of R-bicalutamide was found. The bicalutamide dose that can transfer to a woman by sexual intercourse is small and fluctuates around 0.3 μg/kg. This amount is lower than the dose necessary to cause changes in the offspring of laboratory animals.

5.3 Preclinical safety data
Bicalutamide is a pure and potent androgen receptor antagonist in experimental animals and humans. The main secondary pharmacological action is induction of CYP450 dependent mixed function oxidases in liver. Enzyme induction has not been observed in humans. Target organ changes, including tumour induction (Leydig cells, thyroid, liver) in animals, are clearly related to the primary and secondary pharmacological action of bicalutamide. Enzyme induction has not been observed in man and none of these findings is considered to have relevance to the treatment of patients with prostate cancer. Atrophy of seminiferous tubules is a predicted class effect with antiandrogens and has been observed for all species examined. Full reversal of testicular atrophy was 24 weeks after a 12 month repeated dose toxicity study in rats, although functional reversal was evident in reproduction studies 7 weeks after the end of an 11 week dosing period. A period of subfertility or infertility should be assumed in man.

Genotoxicity studies did not reveal any mutagenic potential of bicalutamide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
lactose monohydrate
Povidone K-29/32
Crospovidone
Sodium laurilsulfate
Magnesium stearate
Coating:
Lactose monohydrate  
Hyromellose  
Titanium oxide (E 171)  
Macrogol 4,000  

6.2 Incompatibilities  
Not applicable.  

6.3 Shelf life  
3 years.  

6.4 Special precautions for storage  
This medicinal product requires no special conditions for storage.  

6.5 Nature and contents of container  
PVC/PE/PVDC/Al blister pack box.  
The packaging contains 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 98, 100, 140, 200 or 280 film-coated tablets.  
Not all pack sizes may be marketed.  

6.6 Special precautions for disposal  
No special requirements.  

7 MARKETING AUTHORISATION HOLDER  
Kiron Pharmaceutica BV  
Sterreschansweg 79  
6522 GM Nijmegen  
The Netherlands  

8 MARKETING AUTHORISATION NUMBER(S)  
PL 22983/0002  

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  
21/04/2009  

10 DATE OF REVISION OF THE TEXT  
21/04/2009  

11 DOSIMETRY (IF APPLICABLE)  

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Bicalutamide 50 mg is and what it is used for
2. Before you take Bicalutamide 50 mg
3. How to take Bicalutamide 30 mg
4. Possible side effects
5. How to store Bicalutamide 50 mg
6. Further information

1. What Bicalutamide 50 mg is and what it is used for
Bicalutamide is an antiandrogen. This means it blocks the actions of male hormones (androgens) in the body. It also reduces the amount of male hormones made in the body.

Bicalutamide 50 mg is used in adult men to treat prostate cancer if you are also taking medicines called luteinising hormone-releasing hormone (LHRH)-analogues e.g. goserelin or have had or will soon have a surgical castration.

2. Before you take Bicalutamide 50 mg

Do not take Bicalutamide 50 mg
- if you are allergic (hypersensitive) to bicalutamide or any of the other ingredients of Bicalutamide 50 mg (see further information for other ingredients).
- if you are female
- if the tablets are to be given to a child
- if you are taking terfenadine or astemizole which are used to treat allergies or cisapride which is used to treat heartburn and acid reflux.

Take special care with Bicalutamide 50 mg
- if you have a liver disease. Your doctor may decide to do blood tests to check your liver is working properly while you are taking this medicine.
- if you have diabetes. Treatment with bicalutamide in combination with luteinising hormone-releasing hormone (LHRH) analogues may alter your blood sugar level. Your dosage of insulin and/or oral antidiabetic medicines may need to be adjusted.

If any of these apply to you and you have not already discussed these with your doctor, talk to your doctor or pharmacist before taking these tablets.

Taking other medicines
Before using bicalutamide, tell your doctor if you are taking, or have recently taken any of the following medicines:
- Cyclosporin (used to suppress the immune system to prevent and treat rejection of a transplanted organ or bone marrow). This is because bicalutamide may increase the concentration of a substance called creatinine in your plasma and your doctor may take blood samples to monitor this.
- Midazolam (a medicine which is used to relieve anxiety before surgery or certain procedures or as an anaesthetic before and during surgery). You must tell your doctor or dentist you are taking bicalutamide if you need an operation or are very anxious in hospital.
- Terfenadine or astemizole which are used to treat allergies or cisapride which is used to treat heartburn and acid reflux (See section 2. Do not take Bicalutamide 50 mg).
- a type of medicine called a calcium channel blocker e.g. diltiazem or verapamil. These are used to treat heart problems, angina and high blood pressure.
- medicines to thin your blood e.g. warfarin.
- Cimetidine for acid reflux or stomach ulcers, or ketoconazole an antifungal medicine.

Please tell your doctor or pharmacist if you are taking or have recently taken any of the medicines listed above or any other medicines, including medicines obtained without a prescription.

Taking Bicalutamide 50 mg with food and drink
The tablets do not need to be taken with food but must be swallowed whole with a glass of water.

Pregnancy and breast-feeding
This medicine must never be taken by women.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine should not affect your ability to drive or use machines however some people may feel sleepy while taking this medicine. If you think your medicine is making you feel sleepy you must talk to your doctor or pharmacist before driving or using machines.

Important information about the ingredients of Bicalutamide 50 mg
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
3. How to take Bicalutamide 50 mg

Always take bicalutamide exactly as your doctor has told you. Check with your pharmacist if you are not sure.

The usual dose of this medicine is one tablet, once a day. This must be swallowed whole with a glass of water. Try to take the medicinal product approximately at the same time each day.

You should start taking these tablets at least 3 days before starting treatment with LHRH analogues e.g. goserelin, or at the same time as undergoing surgical castration.

If you take more Bicalutamide 50 mg than you should
If you think that you may have taken more tablets than you should, contact your doctor or the nearest hospital as soon as possible. Take with you the remaining tablets or the pack so the doctor can identify what you have taken. He or she may decide to monitor your body function until the effects of bicalutamide have worn off.

If you forget to take Bicalutamide 50 mg
If you think that you may have missed a dose of bicalutamide talk to your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose. Just take the normal dose at the usual time.

If you stop taking Bicalutamide 50 mg
Do not stop taking this medicine even if you are feeling well unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, bicalutamide can cause side effects, although not everybody gets them.

If you get any of the following symptoms tell your doctor immediately or go to the casualty department at your nearest hospital. These are very serious side effects:
- Skin rash, itching, hives, peeling, blistering or crusting of the skin
- Swelling of the face or neck, lips, tongue or throat which may cause difficulty in breathing or swallowing
- Breathing problems with or without a cough and fever
- Yellow coloration of the skin or the eyes

Other possible side-effects of the medicine are:
In more than 1 in 10 patients.
Breast soreness • Developments of breasts in males • Hot flushes • Dizziness • Pain in the stomach, chest or pelvis • Constipation • Feeling sick • Presence of blood in the urine (haematuria) • Feeling weak • Swelling of the hands, feet, arms or legs (oedema)

In less than 1 in 10 but more than 1 in 100 patients:
Low numbers of red blood cells (anaemia) • Lower sex drive • Depression • Difficulty in sleeping • Acid indigestion • Wind • Changes to liver function including yellowing of the skin and whites of the eyes (jaundice) • Hair loss • Increased hair growth • Dry skin • Rash • Itching of the skin • Difficulty in gaining an erection • Weight gain • Loss of appetite

In less than 1 in 100 but more than 1 in 1000 patients:
Allergic reactions (hypersensitivity reactions). The symptoms of these may include: skin rash, itching, lumps, peeling, blistering or crusting of the skin, swelling of the face or neck, lips, tongue or throat which may cause difficulty in breathing or swallowing • An inflammation of the lungs called interstitial lung disease. The symptoms of this may include severe breathlessness with a cough or fever

In less than 1 in 10,000 patients:
Liver failure

In addition, cardiac failure was reported in clinical trials during treatment with bicalutamide plus an LHRH analogue.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

5. How to store Bicalutamide 50 mg

Keep out of the reach and sight of children.

Do not use bicalutamide after the expiry date stated on the blister and carton after “EXP”. The first two digits indicate the month and the last four digits indicate the year. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage condition.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Bicalutamide 50 mg contains:
• The active substance is bicalutamide (50 mg).
• The other ingredients in the tablet core are: lactose monohydrate, magnesium stearate, crospovidone, povidone K-29/32, sodium laurilsulfate
The ingredients in the tablet coating are: lactose monohydrate, hypromellose, macrogol 4000, titanium dioxide (E171).

What Bicalutamide 50 mg looks like and contents of the pack
The tablets are white, round, biconvex film-coated tablets, debossed with BCS50 on one side.

They are available in blisters of 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 98, 100, 140, 200 and 280 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Kiron Pharmaceutica BV
Sterreschansweg 79
6522 GM Nijmegen
The Netherlands

Manufacturer:
Synthon Hispania S.L.
Castello 1, Poligono Las Salinas
Sant Boi de Llobregat
Spain
PACKAGE LEAFLET: INFORMATION FOR THE USER

Bicalutamide 150 mg, film-coated tablets
bicalutamide

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Bicalutamide 150 mg is and what it is used for
2. Before you take Bicalutamide 150 mg
3. How to take Bicalutamide 150 mg
4. Possible side effects
5. How to store Bicalutamide 150 mg
6. Further information

1. What Bicalutamide 150 mg is and what it is used for

Bicalutamide belongs to the group of anti-androgens. Anti-androgens act against the effects of androgens (male sex hormones).

Bicalutamide is used in adult men for the treatment of prostate cancer without metastases, when castration or other types of treatment are not indicated or unacceptable.

It may be used in combination with radiotherapy or prostate surgery in early treatment programmes.

2. Before you take Bicalutamide 150 mg

Do not take Bicalutamide 150 mg
• if you are allergic (hypersensitive) to bicalutamide or any of the other ingredients of Bicalutamide 150 mg (see further information for other ingredients).
• if you are female
• if the tablets are to be given to a child
• if you are taking terfenadine or astemizole which are used to treat allergies or cisapride which is used to treat heartburn and acid reflux.
Take special care with Bicalutamide 150 mg

- If you have a liver disease. Your doctor may decide to do blood tests to check your liver is working properly while you are taking this medicine.

If this applies to you and you have not already discussed this with your doctor, talk to your doctor or pharmacist before taking these tablets.

Taking other medicines

Before using bicalutamide, tell your doctor if you are taking, or have recently taken any of the following medicines:

- Cyclosporin (used to suppress the immune system to prevent and treat rejection of a transplanted organ or bone marrow). This is because bicalutamide may increase the concentration of a substance called creatinine in your plasma and your doctor may take blood samples to monitor this.
- Midazolam (a medicine which is used to relieve anxiety before surgery or certain procedures or as an anaesthetic before and during surgery). You must tell your doctor or dentist if you are taking bicalutamide if you need an operation or are very anxious in hospital.
- Terfenadine or astemizole which are used to treat allergies or cisapride which is used to treat heartburn and acid reflux (See section 2, Do not take Bicalutamide 150 mg).
- A type of medicine called a calcium channel blocker e.g. diltiazem or verapamil. These are used to treat heart problems, angina and high blood pressure.
- Medicines to thin your blood e.g. warfarin.
- Cimetidine for acid reflux or stomach ulcers, or ketoconazole an antifungal medicine.

Please tell your doctor or pharmacist if you are taking or have recently taken any of the medicines listed above or any other medicines, including medicines obtained without a prescription.

Taking Bicalutamide 150 mg with food and drink

The tablets do not need to be taken with food but must be swallowed whole with a glass of water.

Pregnancy and breast-feeding

This medicine must never be taken by women.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

This medicine should not affect your ability to drive or use machines however some people may feel sleepy while taking this medicine. If you think your medicine is making you feel sleepy you must talk to your doctor or pharmacist before driving or using machines.

Important information about the ingredients of Bicalutamide 150 mg

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
3. How to take Bicalutamide 150 mg

Always take bicalutamide exactly as your doctor has told you. Check with your pharmacist if you are not sure.

The usual dose of this medicine is one tablet, once a day. This must be swallowed whole with a glass of water. Try to take the medicinal product approximately at the same time each day.

If you take more Bicalutamide 150 mg than you should
If you think that you may have taken more tablets than you should, contact your doctor or the nearest hospital as soon as possible. Take with you the remaining tablets or the pack so the doctor can identify what you have taken. He or she may decide to monitor your body function until the effects of bicalutamide have worn off.

If you forget to take Bicalutamide 150 mg
If you think that you may have missed a dose of bicalutamide talk to your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose. Just take the normal dose at the usual time.

If you stop taking Bicalutamide 150 mg
Do not stop taking this medicine even if you are feeling well unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, bicalutamide can cause side effects, although not everybody gets them.

If you get any of the following symptoms tell your doctor immediately or go to the casualty department at your nearest hospital. These are very serious side effects.

- Skin rash, itching, hives, peeling, blistering or crusting of the skin
- Swelling of the face or neck, lips, tongue or throat which may cause difficulty in breathing or swallowing
- Breathing problems with or without a cough and fever
- Yellow coloration of the skin or the eyes

Other possible side-effects of the medicine are:

In more than 1 in 10 patients:
Rash • Breast soreness • Developments of breasts in males • Feeling weak

In less than 1 in 10 but more than 1 in 100 patients:
Hot flushes • Low numbers of red blood cells (anaemia) • Loss of appetite • Lower sex drive • Depression • Dizziness • Difficulty in sleeping • Pain in the stomach, chest or pelvis • Constipation and wind • Acid indigestion • Feeling sick • Changes to
liver function including yellowing of the skin and whites of the eyes (jaundice) • Hair loss • Increased hair growth • Dry skin • Itching of the skin • Presence of blood in the urine (haematuria) • Difficulty in gaining an erection • Swelling of the hands, feet, arms or legs (oedema) • Weight gain

In less than 1 in 100 but more than 1 in 1000 patients:
Allergic reactions (hypersensitivity reactions). The symptoms of these may include: skin rash, itching, hives, peeling, blistering or crusting of the skin, swelling of the face or neck, lips, tongue or throat which may cause difficulty in breathing or swallowing • An inflammation of the lungs called interstitial lung disease. The symptoms of this may include severe breathlessness with a cough or fever

In less than 1 in 10,000 patients:
Liver failure

In addition, cardiac failure was reported in clinical trials during treatment with bicalutamide plus an LHRH analogue.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Bicalutamide 150 mg

Keep out of the reach and sight of children.

Do not use bicalutamide after the expiry date stated on the blister and carton after ‘EXP’. The first two digits indicate the month and the last four digits indicate the year. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage condition.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Bicalutamide 150 mg contains
• The active substance is bicalutamide (150 mg).
• The other ingredients in the tablet core are: lactose monohydrate, magnesium stearate, crospovidone, povidone K-29/32, sodium laurylsulfate. The ingredients in the tablet coating are: lactose monohydrate, hypromellose, macrogol 4000, titanium dioxide (E171).

What Bicalutamide 150 mg looks like and contents of the pack
The tablets are white, round, biconvex film-coated tablets, debossed with BCM150 on one side.
The tablets are white round, film coated tablets, imprinted with BCM150 on one side. They are available in packs of 5, 7, 10, 14, 20, 28, 30, 40, 50, 56, 80, 84, 90, 98, 100, 140, 200 or 280.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Kiron Pharmaceutica BV
Stenrijnweg 79
6522 GM Nijmegen
The Netherlands

Manufacturer:
Synthon Hispania S.L.
Castello 1, Poligono Las Salinas
Sant Boi de Llobregat
Spain
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton box

1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide 50 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg bicalutamide

3. LIST OF EXCIPIENTS

Tablets also contain lactose: see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

5 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
84 tablets
90 tablets
98 tablets
100 tablets
140 tablets
200 tablets
280 tablets
5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP.: {mm/yyyy}

9. **SPECIAL STORAGE CONDITIONS**

Store in the original package.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Kiron Pharmaceuticals BV
Sterreschansweg 79
6522 GM Nijmegen
The Netherlands

12. **MARKETING AUTHORISATION NUMBER(S)**

PL number 22983/0001
<table>
<thead>
<tr>
<th>13. BATCH NUMBER</th>
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<td>Batch No.:</td>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<th>15. INSTRUCTIONS ON USE</th>
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<tr>
<td>Use as directed by a medical practitioner</td>
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<th>16. INFORMATION IN BRAILLE</th>
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<tr>
<td>Bicalutamide 50 mg film-coated tablets</td>
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<tr>
<td>Bicalutamide 150 mg film-coated tablets</td>
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</table>
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

| PVC/PE/PVDC:Al Blister |

### 1. NAME OF THE MEDICINAL PRODUCT

Bicalutamide 50 mg film-coated tablets

### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Kiron Pharmaceutica BV

### 3. EXPIRY DATE

EXP.: {mm/yyyy}

### 4. BATCH NUMBER

Batch No.: 

### 5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box

1. **NAME OF THE MEDICINAL PRODUCT**

Bicalutamide 150 mg film-coated tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 150 mg bicalutamide

3. **LIST OF EXCIPIENTS**

Tablets also contain lactose: see leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

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5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.: {mm/yyyy}

9. SPECIAL STORAGE CONDITIONS

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kiron Pharmaceutica BV
Sterreschansweg 79
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12. MARKETING AUTHORIZATION NUMBER(S)

PL number 22983/0002

13. BATCH NUMBER

Batch No.: 

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by a medical practitioner

16. INFORMATION IN BRAILLE

Bicalutamide 150 mg film-coated tablets

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