BICALUTAMIDE 50MG TABLETS
(bicalutamide)

PL 24668/0024

UK Public Assessment Report

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Limited a Marketing Authorisation (licence) for the medicinal product Bicalutamide 50mg Tablets (PL 24668/0024) on 5th November 2008. This is a prescription-only medicine (POM), used in the treatment of prostate cancer.

Bicalutamide 50mg Tablets contain the active ingredient bicalutamide, which belongs to a group of medicines called anti-androgens. It interferes with some of the actions of androgens (male sex hormones) within the body.

The test product was considered to be a generic version of the reference product Casodex Tablets 50mg (AstraZeneca UK Limited) based on data submitted by Caduceus Pharma Limited.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Bicalutamide 50mg Tablets outweigh the risk; hence a Marketing Authorisation (MA) has been granted.

BICALUTAMIDE 50MG TABLETS
(bicalutamide)

PL 24668/0024

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Caduceus Pharma Limited a Marketing Authorisation for the medicinal product Bicalutamide 50mg Tablets (PL 24668/0024) on 5th November 2008. The product is a prescription-only medicine (POM) indicated for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Casodex Tablets 50mg (PL 17901/0005; AstraZeneca UK Limited) originally authorised to Zeneca Limited (as PL 12619/0102) on 23rd February 1995. The innovator product has been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Bicalutamide is a non-steroidal anti-androgen. 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 anti-androgen withdrawal syndrome in a subset of patients. Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

The application is supported by the bioequivalence study presented by the applicant comparing the test product Bicalutamide 50mg Tablets with the reference product Casodex Tablets 50mg (AstraZeneca Limited).

PHARMACEUTICAL ASSESSMENT

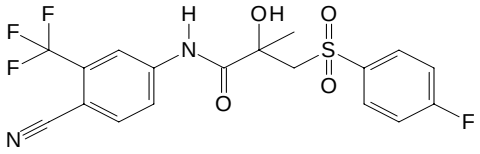
ACTIVE SUBSTANCE

Bicalutamide

Nomenclature:

INN:	Bicalutamide
Chemical names:	● N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl) suphonyl]-2-hydroxy-2-methylpropanamide. ● 4-Cyano-3-trifluoromethyl-N-(3-p-fluoro-phenylsulfonyl-2-hydroxy-2-methylpropionyl)aniline ● ±-4'-Cyano-α, α, α-trifluoro-3-[(p-fluorophenyl)sulphonyl]-2-methyl-m-lactotoluidide

Structure:



Molecular formula:	$C_{18}H_{14}F_4N_2O_4S$
Molecular weight:	430.38
CAS No:	90357-06-5
Physical form:	A white to off-white powder
Solubility:	It is soluble in acetone and N,N-dimethylformamide and sparingly soluble in methanol. It is also insoluble in water and buffer solutions. It has a melting point of about 193°C.
Polymorphism:	Polymorphism exhibited; three known forms.
Stereochemistry:	The drug substance is a racemate with zero specific optical rotation.

The active substance, bicalutamide, is not the subject of a British Pharmacopeia (BP) or European Pharmacopeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in two polyethylene (PE) bags; a transparent PE bag placed inside an opaque PE bag. The bags are tied separately with plastic tags and placed into HDPE (high density polyethylene) drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polythene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 5 years.

DRUG PRODUCT

Composition

The drug product is a direct-release film-coated tablet containing 50mg of the active substance, bicalutamide. The tablets are white, round, biconvex, with the marking “B 50” on one side.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, sodium starch glycolate (Type A), povidone K-30 and magnesium stearate making up the tablet core; and titanium dioxide (E171), polyethylene glycol, polyvinyl alcohol and talc constituting ‘Opadry II 85F 18422 white’ which makes up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of Opadry II 85F 18422 white which makes up the tablet coating, and complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Satisfactory comparative dissolution data were provided for the test and reference products. The dissolution profiles were found to be similar.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 reference standards used.

Container Closure System

The finished product is licensed for marketing in PVC (polyvinylchloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 10, 14, 28, 30, 40, 50, 60, 90, or 100 tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. There are no special storage instructions.

Bioequivalence Study

A bioequivalence study was submitted comparing the test product, Bicalutamide 50mg Tablets, to the innovator product, Casodex Tablets 50mg (AstraZeneca Limited).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

Conclusion

The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. On this basis, and considering the bioequivalence data provided, the applicant's claim that Bicalutamide 50mg Tablets is a generic medicinal product of Casodex Tablets 50mg appears justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation was therefore granted.

PRECLINICAL ASSESSMENT

This abridged application, submitted under Article 10.1 of Directive 2001/83/EC, as amended, is for Bicalutamide 50mg Tablets, claiming to be a generic medicinal version of Casodex Tablets 50mg (AstraZeneca UK Limited).

No new preclinical data have been supplied with this application and none are required for applications of this type. A preclinical overview has been written by a suitably qualified expert and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Bicalutamide 50mg Tablets are indicated for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

The indications are consistent with those for the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator product.

PAEDIATRIC DEVELOPMENT PROGRAMME

Bicalutamide is contraindicated in children.

TOXICOLOGY

No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Bicalutamide is a non-steroidal anti-androgen, devoid of 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 anti-androgen withdrawal syndrome in a subset of patients.

Bicalutamide is a racemate with its anti-androgenic activity being almost exclusively in the (R)-enantiomer.

Pharmacokinetics

Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability. The (S)-enantiomer is rapidly cleared relative to the (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week.

On daily administration of Bicalutamide, the (R)-enantiomer accumulates about 10 fold in plasma as a consequence of its long half-life. The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment.

Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

Bioequivalence Study

The bioequivalence study compared the test product, Bicalutamide 50mg Tablets, to the reference product Casodex Tablets 50mg (AstraZeneca Limited). Satisfactory Certificates of Analysis for the test and reference products were provided. The study was conducted in accordance with current standards of Good Clinical Practice.

The design was a randomised, open-label, two-treatment, two-period, parallel, single dose bioequivalence study, performed in 48 healthy adult human volunteers under fasting conditions. A single dose of the 50mg bicalutamide test or reference formulation was administered orally, with water, to each subject in each period, after an overnight fast of 10 hours. A satisfactory washout period was maintained between the two dosing days in each group.

Blood samples were collected at 16 time points up to 120 hours post-dose. The plasma samples were assayed for bicalutamide using a validated liquid chromatographic - mass spectrometric analytical method

An adequate statistical plan was provided. The test product was compared to the reference product with respect to the pharmacokinetic variables C_{max} and AUC_{0-120} using ANOVA.

Biostudy outcome and results:

Statistical and pharmacokinetic analyses were performed on data from 47 subjects. The summary of the results of the bioequivalence study are tabulated below.

Pharmacokinetic results for a randomised single dose 2-way crossover study between the test and reference products. n=47 healthy subjects, dosed fasted; t=120 hours.

	Bicalutamide 50 mg (Test)	**Casodex 50 mg (Reference)**	**Test/Ref (90% CI)**
AUC_{0-120} (ng.hr/ml)	11.30	11.31	0.99 (0.92 – 1.07)
C_{max} (ng/ml)	6.72	6.75	0.97 (0.90 – 1.04)

The 90% confidence intervals for the ln-transformed parameters C_{max} and AUC_{0-t} for bicalutamide lie within the range 80.0 – 125.0%, such that the test and reference products may be considered bioequivalent after a single dose under fasted conditions.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

SAFETY

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical overview. The reference product is established and the main basis of the application depends upon the bioequivalence study.

There were no deaths, serious adverse events, or other significant adverse events in the bioequivalence study.

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The final SmPC is consistent with that for the innovator product, and it is acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

DISCUSSION AND CONCLUSION

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Bicalutamide 50mg Tablets) and reference (Casodex Tablets 50mg, AstraZeneca Limited) products within general acceptance limits.

Sufficient clinical information has been submitted to support this application. When used as indicated, Bicalutamide 50mg Tablets has a favourable benefit-to-risk ratio. The grant of a Marketing Authorisation was, therefore, recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Bicalutamide 50mg 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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Bicalutamide 50mg Tablets and the reference product; Casodex Tablets 50mg (AstraZeneca Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with that for Casodex Tablets 50mg.

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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed. However, they have committed to submitting mock-ups for all packaging for assessment before they are commercially marketed.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with bicalutamide is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

BICALUTAMIDE 50MG TABLETS

(bicalutamide)

PL 24668/0024

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation application on 19th January 2007

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 6th March 2007

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 5th June 2007 and further information relating to the clinical dossier on 20th August 2007

4 The applicant responded to the MHRA's request, providing further information for the quality sections on 26th October 2007 and further information for the clinical sections on 1st November 2007

5 Upon review of responses, the MHRA requested further information relating to the quality sections on 5th March 2008

6 The applicant responded to the MHRA's request, providing further information for the quality sections on 18th April 2008

7 The application was determined on 5th November 2008

BICALUTAMIDE 50MG TABLETS
(bicalutamide)

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STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Bicalutamide 50mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide 50mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg bicalutamide

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex, 7mm diameter. Marked ‘B 50’ on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adult males including the elderly: one tablet (50mg) once a day.

Treatment with Bicalutamide 50mg Tablets should be started at least 3 days before commencing treatment with an LHRH analogue, or at the same time as surgical castration.

Children: Bicalutamide is contraindicated in children.

Renal impairment: no dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment: no dosage adjustment is necessary for patients with mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe hepatic impairment (see section 4.4).

4.3 CONTRAINDICATIONS

Bicalutamide 50mg Tablets must not be given to any patient who has a known hypersensitivity to Bicalutamide or to any of the excipients.

Bicalutamide 50mg Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Bicalutamide is contraindicated in females and children.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 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). Therefore, caution should be exercised when Bicalutamide is co-administered with drugs metabolised predominantly by CYP 3A4 (see sections 4.3 and 4.5).

Lactose sensitive patients should be aware that each Bicalutamide 50 mg Tablet contains 57 mg of lactose monohydrate.

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 contra-indicated 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 sites. 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 50 mg Tablets are 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

Bicalutamide in general, has been well tolerated with few withdrawals due to adverse events.

Table 1 Frequency of Adverse Reactions

Frequency	System Organ Class	Event
Very common (≥ 10%)	Reproductive system and breast disorders	Breast tenderness[1] Gynaecomastia[1]
	General disorders	Hot flushes[1]
Common (≥ 1% and < 10%)	Gastrointestinal disorders	Diarrhoea Nausea
	Hepato-biliary disorders	Hepatic changes (elevated levels of transaminases, cholestasis and jaundice)[2]
	General disorders	Asthenia Pruritus
Uncommon (≥ 0.1% and < 1%)	Immune system disorders	Hypersensitivity reactions, including angioneurotic oedema and urticaria
	Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Rare (≥ 0.01% and < 0.1%)	Gastrointestinal disorders	Vomiting
	Skin and subcutaneous tissue disorders Hepato- biliary disorders	Dry skin Hepatic failure[3]

[1] May be reduced by concomitant castration.

[2] Hepatic changes are rarely severe and were frequently transient, resolving or improving with continued therapy or following cessation of therapy (see section 4.4 Special warnings and special precautions for use).

[3] Hepatic failure has occurred very 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).

Rare cardiovascular effects such as angina, heart failure, conduction defects including PR and QT interval prolongations, arrhythmias and non-specific ECG changes have been observed.

Thrombocytopenia has been reported rarely.

In addition, the following adverse experiences were reported in clinical trials (as possible adverse drug reactions in the opinion of investigating clinicians, with a frequency of ≥1%) during treatment with Bicalutamide plus an LHRH analogue. No causal relationship of these experiences to drug treatment has been made and some of the experiences reported are those that commonly occur in elderly patients:

Cardiovascular system: heart failure.

Gastrointestinal system: anorexia, dry mouth, dyspepsia, constipation, flatulence.

Central nervous system: dizziness, insomnia, somnolence, decreased libido.

Respiratory system: dyspnoea.

Urogenital: impotence, nocturia.

Haematological : anaemia.

Skin and appendages: alopecia, rash, sweating, hirsutism.

Metabolic and nutritional: diabetes mellitus, hyperglycaemia, oedema, weight gain, weight loss.

Whole body: abdominal pain, chest pain, headache, pain, pelvic pain, chills.

4.9 OVERDOSE

There is no human experience of overdosage. 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-androgensATC code: L02BB03

Bicalutamide is a non-steroidal anti-androgen, devoid of 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 anti-androgen withdrawal syndrome in a subset of patients.

Bicalutamide is a racemate with its anti-androgenic activity being almost exclusively in the (R)-enantiomer.

5.2 PHARMACOKINETIC PROPERTIES

Bicalutamide is well absorbed following oral administration. There is no evidence of any clinically relevant effect of food on bioavailability.

The (S)-enantiomer is rapidly cleared relative to the (R)-enantiomer, the latter having a plasma elimination half-life of about 1 week.

On daily administration of Bicalutamide, the (R)-enantiomer accumulates about 10 fold in plasma as a consequence of its long half-life.

Steady state plasma concentrations of the (R)-enantiomer of approximately 9 microgram/ml are observed during daily administration of 50 mg doses of Bicalutamide. At steady state the predominantly active (R)-enantiomer accounts for 99% of the total circulating enantiomers.

The pharmacokinetics of the (R)-enantiomer are unaffected by age, renal impairment or mild to moderate hepatic impairment. There is evidence that for subjects with severe hepatic impairment, the (R)-enantiomer is more slowly eliminated from plasma.

Bicalutamide is highly protein bound (racemate 96%, R-bicalutamide 99.6%) and extensively metabolised (via oxidation and glucuronidation): Its metabolites are eliminated via the kidneys and bile in approximately equal proportions.

5.3 PRECLINICAL SAFETY DATA

Bicalutamide is a potent anti-androgen and a mixed function oxidase enzyme inducer in animals. Target organ changes, including tumour induction, in animals, are related to these activities. None of the findings in the preclinical testing is considered to have relevance to the treatment of advanced prostate cancer patients.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Bicalutamide 50mg Tablets include the following excipients:

Tablet Core:

Lactose monohydrate

Sodium starch glycolate (Type A)

Povidone K-30

Magnesium Stearate

Film Coating Material:

Opadry II 85F 18422 white containing:

Polyethylene glycol

Polyvinyl alcohol

Talc E553b

Titanium dioxide E171

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

Bicalutamide 50mg Tablets have a shelf-life of 24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Bicalutamide 50mg Tablets are provided in Aluminium Foil/PVC blister packs of 10, 14, 28, 30, 40, 50, 60, 90, or 100 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

8th Floor,

94 Wigmore Street,

London

W1U 3RF

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 24668/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5th November 2008

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Bicalutamide 50mg Tablets

Caduceus PHARMA LTD

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 you doctor or pharmacist.

In this leaflet:

1 What Bicalutamide 50mg Tablets are and what they are used for

Bicalutamide belongs to a group of medicines called anti-androgens. This means that it interferes with some of the actions of androgens (male sex hormones) within the body.
Bicalutamide 50mg Tablets are used to treat prostate cancer.

You should not take Bicalutamide if you are pregnant or are breast feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Bicalutamide 50mg Tablets are unlikely to affect your ability to drive or to operate machinery. However, some people may occasionally feel drowsy when taking Bicalutamide. If this happens to you, you should exercise caution when carrying out such tasks.

Important information about some of the ingredients of Bicalutamide 50mg Tablets
This medicine contains lactose. 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 50mg Tablets

Always take Bicalutamide 50mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual dose is one tablet taken daily.
Swallow the tablet whole with a drink of water.
Bicalutamide 50mg Tablets can be taken with food or on an empty stomach.
Try to take your tablet at the same time each day.

If you take more Bicalutamide 50 mg Tablets than you should:

2 Before you take Bicalutamide 50mg Tablets

Bicalutamide must not be taken by women, including pregnant women or mothers who are breast feeding.
Bicalutamide must not be given to children.

Also, do not take Bicalutamide 50mg Tablets:
- if you are allergic (hypersensitive) to Bicalutamide or any of the other ingredients of Bicalutamide 50mg Tablets.

Take special care with Bicalutamide 50mg Tablets:
- if you have liver problems. You should inform your doctor before treatment as he/she needs to take special care.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
In particular, tell your doctor if you are taking any of the following:
- oral anticoagulants (to prevent blood clots)
- terfenadine (an antihistamine)
- astemizole (an antihistamine)
- cisapride (for some types of indigestion)
- ciclosporin (to suppress your immune system)
- calcium channel blockers (to treat high blood pressure or some heart conditions).
- cimetidine (to treat heartburn and stomach ulcers)
- ketoconazole (to treat fungal infections of the skin and nails)

Pregnancy and breast feeding
Bicalutamide must not be taken by women.

If you take more than your normal dose, contact your doctor.
In the case of an overdose, contact the nearest hospital immediately.

If you forget to take a Bicalutamide 50mg Tablet:
You should take Bicalutamide 50mg Tablets as prescribed. However, if you forget to take your medicine, take your dose when you remember and then take your next dose at the usual time. Don't take a double dose to make up for a forgotten tablet. If you are worried, ask your doctor or pharmacist for advice.
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.

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 50mg Tablets can cause side effects, although not everybody gets them.
Contact your doctor or seek medical help immediately if you experience any of the following:
- Serious breathlessness, or sudden worsening of breathlessness, possibly with a cough or fever. Some patients taking Bicalutamide get an inflammation of the lungs called interstitial lung disease. This side effect is uncommon.
- Severe itching of the skin (with raised lumps) or swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing. These reactions to Bicalutamide are uncommon.

Tell your doctor if any of the following side effects bother you:

Very common side effects:
- Tender or enlarged breast tissue
- Hot flushes

Common side effects:
- Nausea
- Diarrhoea
- Itching
- Feeling weak
- Yellow skin or eyes (jaundice)

Rare side effects:
- Vomiting
- Dry skin
- Chest pain or palpitations

Bicalutamide 50mg Tablets may occasionally be associated with changes in your blood which may require your doctor to do certain blood tests.
Do not be alarmed by this list of possible effects. You may not have any of them.
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 50mg Tablets

This medicinal product does not require any special storage conditions.
Keep out of the reach and sight of children.
Do not use Bicalutamide 50mg Tablets after the expiry date which is stated on the carton and container/blister strips.
Keep the tablets in the container that they came in.
If your doctor decides to stop treatment, return any left-over tablets to your pharmacist. Only keep them if the doctor tells you to.
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 50mg Tablets contain
- The active substance is Bicalutamide 50mg.

- The other ingredients are:

Lactose monohydrate
Sodium starch glycolate (Type A)
Povidone K-30
Magnesium Stearate
Opadry II 85F 18422 white

What Bicalutamide 50mg Tablets look like and contents of the pack
Bicalutamide 50mg Tablets are film-coated, white, round, biconvex 7mm tablets marked with 'B 50' on one side.

Pack sizes:

*(only the actual marketed pack sizes will be stated on the leaflet)

Bicalutamide 50mg Tablets are supplied in blister packs of 10, 14, 28, 30, 40, 50, 60, 90, or 100 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
CADUCEUS PHARMA LIMITED
8th Floor
94 Wigmore street
London
W1U 3RF
UK

Manufacturer:

Actavis Nordic A/S
Ørnegardsvej 16
DK-2820 Gentoffe
Denmark

This leaflet was approved in {MM/YYYY}

LABELLING

Carton for blisters, with braille. Pack size 28.

Braille

Blister foil