Safeguarding public health

Public Assessment Report

Decentralised Procedure

Bicalutamide 50mg tablets
Bicalutamide

UK/H/896/01/DC

UK licence no: PL 16924/0061

Applicant: Qualiti (Burnley) Limited

LAY SUMMARY

The MHRA granted Quality Burnley Limited Marketing Authorisation (licence) for the medicinal product Bicalutamide 50mg tablets on 4th of January 2007. This is a prescription-only medicine (POM) that is used for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

Bicalutamide is a non-steroidal anti-androgen which blocks the actions of Androgen (male sex hormone) released naturally in your body. Bicalutamide can help treat cancer of the prostate gland.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Bicalutamide 50mg film-coated tablets outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Bicalutamide 50mg film-coated tablets
Type of Application	Generic, Article 10.1
Active Substance	Bicalutamide
Form	Film-Coated Tablets
Strength	50mg Film-Coated Tablets
MA Holder	Qualiti (Burnley) Limited Talbot Street, Briercliffe, Burnley, Lancashire, BB10 2JY
RMS	UK
CMS	AT, EL, SI, SK
Procedure Number	UK/H/896/01/DC
Timetable	Day 120– 13 December 2006

Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bicalutamide 50mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg Bicalutamide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White round, bi-convex, film-coated tablet with ‘BIC 50’ on one side and ‘G’ on the other.

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 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 contra-indicated 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 is contra-indicated in females and children.

Bicalutamide tablets must not be given to any patient who has shown a hypersensitivity reaction to the active substance or any of the excipients.

Co-administration of terfenadine, astemizole or cisapride with Bicalutamide is contra-indicated.

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 tablets 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 tablets (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 galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Bicalutamide tablets.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence of any pharmacodynamic or pharmacokinetic interactions between Bicalutamide tablets 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 tablets, mean midazolam exposure (AUC) was increased by up to 80%, after co-administration of Bicalutamide tablets 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 cyclosporin and calcium channel blockers. Dosage reduction may be required for these drugs particularly if there is evidence of enhanced or adverse drug effect. For cyclosporin, 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 tablets 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 tablets 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 contra-indicated 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

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 tablets, 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 ≥ 1during 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: Antiandrogens, ATC code: L02 B B03

Bicalutamide is a non-steroidal antiandrogen, 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 tablets can result in antiandrogen withdrawal syndrome in a subset of patients.

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

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 t, 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 antiandrogen 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

Tablet Core
Lactose monohydrate
Povidone K-29/32
Sodium starch glycollate
Magnesium stearate

Film Coating
Lactose monohydrate
Hypromellose 15cp (E464)
Titanium dioxide (E171)
Glycerol triacetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVdC coated PVC blister strips with aluminium foil lidding. Pack sizes 28, 30, 40, 90 and 100.

Polypropylene tablet container with polyethylene lid (Securitainers). Pack sizes 28, 30, 100, 500 and 1000.

Al/Al blisters. Pack sizes 28, 30, 40, 90 and 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Qualiti (Burnley) Limited
Talbot Street, Briercliffe,
Burnley,
Lancashire BB10 2JY
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16924/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/01/2007

10 DATE OF REVISION OF THE TEXT

04/01/2007

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

BICALUTAMIDE 50 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 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

The name of your medicine is Bicalutamide 50 mg Film-Coated Tablets (referred to as Bicalutamide throughout this leaflet).

1. WHAT BICALUTAMIDE IS AND WHAT IT IS USED FOR

Your medicine comes as a 'film-coated' tablet containing the active ingredient bicalutamide. The other ingredients are listed in section 6 of this leaflet. Bicalutamide is a non-steroidal anti-androgen which blocks the actions of Androgen (male sex hormone) released naturally in your body. Bicalutamide can help treat cancer of the prostate gland.

2. BEFORE YOU TAKE BICALUTAMIDE

Do not take Bicalutamide:
- if you are **allergic (hypersensitive) to bicalutamide or any of the other ingredients** of Bicalutamide 50mg Film-Coated Tablets
- if you are already taking other medicines such as antihistamines (Terfenadine, Astemizole) or Cisapride (for some types of indigestion).
- Bicalutamide treats a condition found only in men. It must not be given to women or children.

Take special care with Bicalutamide:
- if you have liver problems
- if you have an intolerance to some sugars, as this medicine contains lactose.

Tell your doctor if any of the above applies to you.

Taking other medicines
Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The following medicines are known to interact with Bicalutamide:
- Cimetidine, for heartburn or gut ulcers
- Ketoconazole, anti-fungal medicine
- an antihistamine eg. Terfenadine, Astemizole
- Cisapride
- Ciclosporin
- Warfarin, to thin the blood
- medicine to treat high blood pressure or a heart condition called calcium channel blockers.

Taking Bicalutamide with food and drink
Bicalutamide can be taken with or without food.

Pregnancy and breast feeding
Bicalutamide should not be prescribed to women and should not be given to pregnant or breast feeding mothers.

Driving and using machines
Bicalutamide should not affect your ability to drive or use machines. However if Bicalutamide does make you feel sleepy, do not drive or use machines.

Important information about some of the ingredients of Bicalutamide Film-Coated Tablets
Bicalutamide Film-Coated Tablets contain **lactose monohydrate**. If you have been told by your doctor that you have an **intolerance to some sugars**, such as lactose, contact your doctor before taking this medicine.

3. HOW TO TAKE BICALUTAMIDE

- Follow your doctor's instructions exactly. You should check with your doctor or pharmacist if you are not sure
- Take the tablets with a glass of water
- Do not chew the tablets
- Try to take them at the same time each day.

Adults (including the elderly)
Swallow one tablet daily, with or without food. You may also be having other medicine by injection (Gonadorelin treatment) unless you have had your testes removed (castrated).

Children
Bicalutamide must not be given to children.

Patients with liver problems
If you have liver problems your doctor will arrange for you to have regular blood tests.

If you take more Bicalutamide than you should
If you take too much of your medicine, tell your doctor immediately or go to your nearest casualty department.

If you forget to take a dose of Bicalutamide
Take it as soon as you remember unless it is almost time for your next dose. If this happens, skip the missed dose and take the next dose on time. Do not double the dose.

If you stop taking Bicalutamide
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 medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Serious side effects
Tell your doctor straight away or go to your nearest hospital casualty department right away if you have any of the following side effects:
- swelling of the lips, tongue or face or have difficulty breathing or swallowing
- a rash, swollen itchy skin.

You may be allergic (hypersensitive) to this medicine. These effects are uncommon.

Very common side effects (seen in more than 1 in 10 patients) include:
enlarged or tender breasts and hot flushes.

Common side effects (seen in more than 1 in 100 patients but less than 1 in 10 patients) include:
diarrhoea, feeling sick, yellowing of the skin or whites of the eyes, dark urine, raised liver enzyme levels in the blood, feeling weak or itchy.

Uncommon side effects (seen in more than 1 in 1,000 but less than 1 in 100 patients) include:
lung probelms.

Rare side effects (seen in more than 1 in 10,000 patients but less than 1 in 1,000) include:
dry skin, being sick, severe liver problems, angina, changes in heart rhythm, heart failure and unusual bruising or bleeding.

The following side effects have been seen in clinical trials with patients taking Bicalutamide with Gonadorelin treatment, but it is not known if these effects are caused by Bicalutamide: Lack of appetite, dry mouth, indigestion, constipation, wind, feeling dizzy, sleep changes, lack of sex drive, impotence, passing urine in the night, breathlessness, anaemia, hair loss or excessive growth, rash, sweating, diabetes, raised blood glucose levels, swelling of the face, hands or feet, weight change, stomach, pelvic or chest pain, general pain, headache and chills.

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

5. HOW TO STORE YOUR MEDICINE

Keep this medicine out of the reach and sight of children. Store this medicine below 30°C. Do not use Bicalutamide after the expiry date shown on the pack. The expiry date refers to the last day of the month.

6. FURTHER INFORMATION

What Bicalutamide Film-Coated Tablets contain - Each tablet contains 50 mg of the active ingredient bicalutamide. It also contains lactose monohydrate, povidone, sodium starch glycolate, magnesium stearate, hypromellose (E464), titanium dioxide (E171) and glycerol triacetate.

What Bicalutamide Film-Coated Tablets look like and contents of the pack - The tablets are white, round and marked 'BIC 50' on one side and 'G' on the other. Bicalutamide Film-Coated Tablets are available in blister packs of 28, 30, 40, 90 and 100 tablets, and plastic bottles of 28, 30, 100, 500 and 1,000 tablets.

The Marketing Authorisation Holder is:
Qualiti (Burnley) Limited, Talbot Street, Briercliffe, Burnley, Lancashire BB10 2JY, United Kingdom.

The Manufacturers are:
Generics [UK] Ltd., Station Close, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.
McDermott Laboratories Ltd. T/A Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria
Bicalutamid "Arcana" 50 mg - Filmtabletten

Greece
Bicalutamide/Qualiti

Slovak Republic
BICALUTAGEN 50 mg

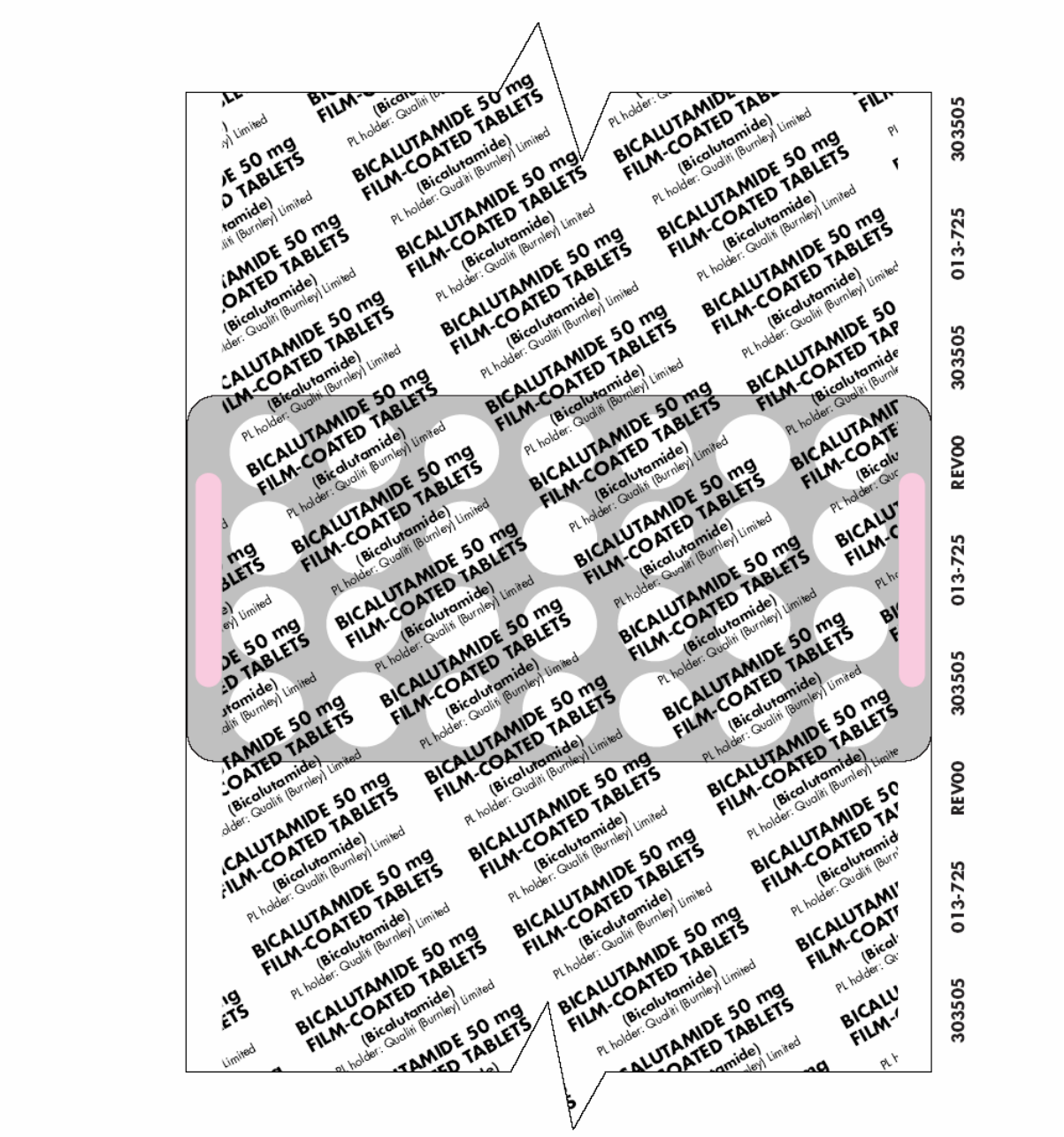
Slovenia
Bickam

United Kingdom
Bicalutamide 50 mg Film-Coated Tablets.

Date of leaflet preparation: December 2006 013-722 IEV00 303506

Module 4

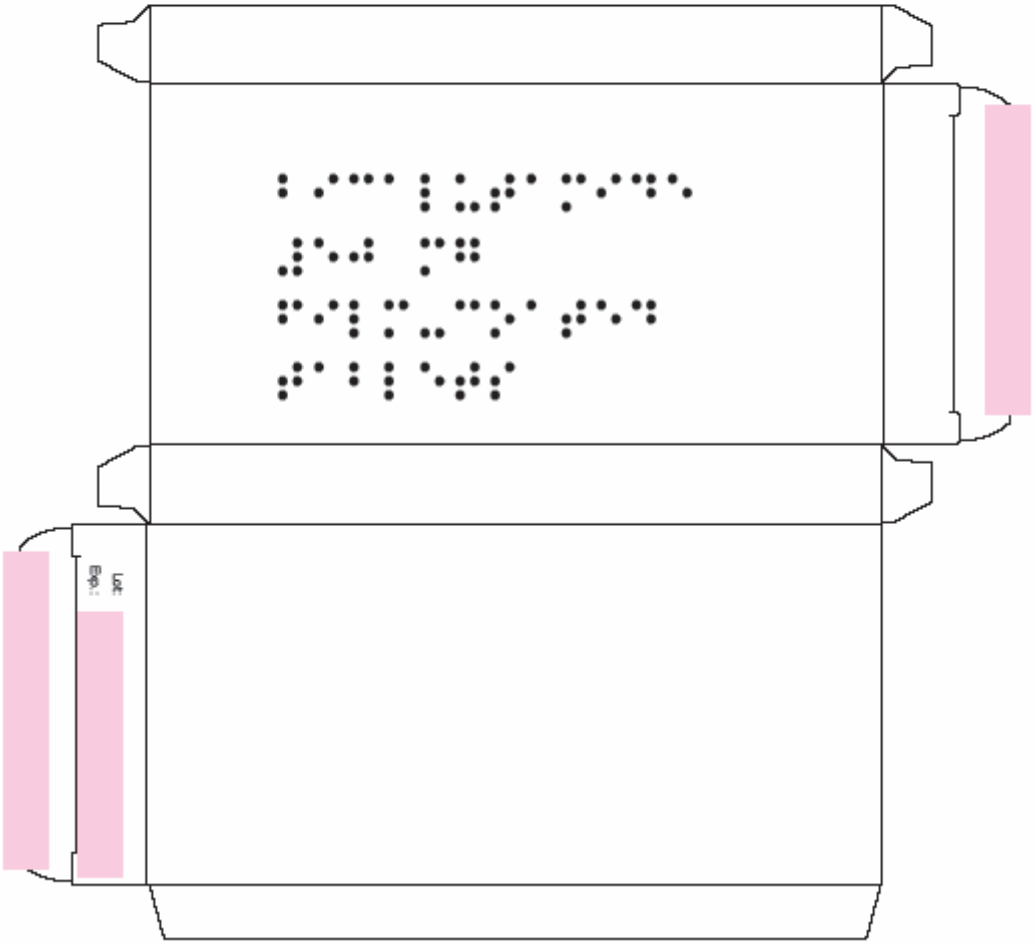
Labelling




Bicalutamide 50 mg Film-Coated Tablets (Bicalutamide)
28 Tablets
50 mg
Bicalutamide 50 mg Film-Coated Tablets
(Bicalutamide)
28 Tablets
Bicalutamide 50 mg Film-Coated Tablets (Bicalutamide)
28 Tablets
Bicalutamide 50 mg Film-Coated Tablets (Bicalutamide)
28 Tablets
Each tablet contains: 50 mg Bicalutamide. Contains: lactose.
For oral use. Use as directed by a doctor. Read the package leaflet before use.
Keep out of the reach and sight of children.
Swallow the tablets whole.
Store below 30°C.
PL 16924/0061 POM 303504
PL Holder: Qualtil (Burnley) Limited, Talbot Street, Brierclffe, Burnley, Lancashire BB10 2JY, United Kingdom.
Distributed by: Generics [UK] Ltd, Potters Bar, Herts, EN6 1TL.
5 016695 001647
MERCK generics

INSTRUCTION TO PRINTERS - ONLY THIS PART OF THE DESIGN TO BE USED FOR BRAILLE EMBOSSING

Braille translation
Bicalutamide
#50 mg
Film-Coated
Tablets



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Bicalutamide 50 mg film-coated tablets, in the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration, could be approvable.

This decentralised application concerns a generic version of bicalutamide submitted under Article 10.1. The originator product is Casodex® 50 mg Tablets by AstraZeneca UK Ltd, registered in the EU since 23rd February 1995.

With UK as the Reference Member State in this Decentralised Procedure, Qualiti (Burnley) Limited is applying for the Marketing Authorisations for Bicalutamide 50 mg film-coated tablets in Austria, Greece, Slovakia and Slovenia.

Bicalutamide is a non-steroidal antiandrogen, which binds to androgen receptors in the prostate and prevents the physiological effects of dihydrotestosterone. Bicalutamide 50 mg film-coated tablets are indicated for the treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration.

The submitted dossier is of acceptable standards.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Bicalutamide 50mg Film-Coated Tablet
Name(s) of the active substance(s) (INN)	bicalutamide
Pharmacotherapeutic classification (ATC code)	Antiandrogens (L02 BB03)
Pharmaceutical form and strength(s)	50mg Film-Coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/896/01/DC
Reference Member State	United Kingdom
Member States Concerned	AT, EL, SI, SK
Marketing Authorisation Number(s)	PL 16924/0061
Name and address of the authorisation holder	Qualiti (Burnley) Limited, Talbot Street, Briercliffe, Burnley, Lancashire BB102JY, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

The chemical-pharmaceutical documentation and Expert Report in relation to bicalutamide 50mg film-coated tablets are of sufficient quality in view of the present European regulatory requirements. The active substance bicalutamide is not described in the European Pharmacopeia. An EDMF and relevant letter of access has been submitted to MHRA. The drug substance specification for drug substance is generally acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period is 48 months and is considered acceptable.

P Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three 130,000 tablet batches. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life is 24 months when stored below 30^{o}C is acceptable.

III.2 PRE-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of bicalutamide are well known. As bicalutamide is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. There are no objections to approval of Bicalutamide 50 mg film-coated tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

To support the application, the applicant has submitted one bioequivalence study to determine the relative rate and extent of absorption and therefore the bioequivalence of two formulations of bicalutamide.

Bioequivalence study

Study design

This study was a randomised, 2-treatment, 1-period, open label, parallel design conducted at the clinical site of SFBC Anapharm. The clinical phase was undertaken from 26th November to 22nd December 2005 and the study was conducted according to GCP.
A randomised crossover design is typically employed in bioequivalence studies. However, due to the long half-life of bicalutamide (the mean elimination half-life ranged from 110 to 140 hours), it was not considered to be appropriate for this study. Thus, a parallel study was conducted. Given the positive evidence of human foetal risk associated with the use of bicalutamide, females were not included in this study.

A single 50 mg dose (1 x 50 mg film-coated tablet) was orally administered with 240 ml of water in the morning. The volunteers were allocated to the study medications according to the randomisation scheme. The subjects were required to fast overnight for at least 10 hours before dosing until at least 4 hours after drug administration. Volunteers were housed for at least 10 hours prior to drug administration until 48 hour post-dose. Blood was collected prior to and at 2.00, 4.00, 8.00, 12.0, 16.0, 20.0, 22.0, 24.0, 26.0, 28.0, 30.0, 32.0, 34.0, 36.0, 38.0, 48.0, 72.0, 96.0, 168, 336, 504, and 624 hours after drug administration.

Assessor's comment

The applicant has justified the use of a parallel design and the exclusion of female subjects. The study design is considered adequate and in line with current guidelines.

Test and reference products

Bicalutamide 50 mg (test) has been compared to Casodex® 50 mg (reference).

Population studied

Fifty healthy male subjects aged 20 to 55 years were included in the study. Forty nine subjects completed the study and the results of these subjects were considered in the statistical analysis as per protocol. One subject in the bicalutamide group withdrew 6 hours after receiving the study drug for personal reasons.

Analytical methods

The experimental samples were assayed for bicalutamide using a liquid chromatography method with mass spectrometric detection, developed and validated in the laboratory of the Analytical Facility. Analysts were blinded about which of the formulations was administered during each period.

Pharmacokinetic Variables

AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el} and $T^{½}$ were evaluated.

Statistical methods

ANOVA was performed on the ln-transformed data of AUC_{0-T}, AUC_{0-inf} and $C_{max.}$ ANOVA was also carried out on the untransformed data of T½el and Kel. A non-parametric test (Wilcoxon's Rank-sum test) to compare the Tmax between treatments was performed and a 90% non parametric confidence interval was calculated.

Results

	TEST **Mean ± SD** **n=24**	**REFERENCE** **Mean ± SD** **n=25**	**Ratio Least Squares Means (%)**	**P-value of F Ratio (formulation difference)**	**90% Geometric Confidence Interval**
C_{max} (ng/ml)	852.19 ± 122.74 [845.57]	801.71 ± 110.65 [788.93]	106.20	0.1544	99.05 to 113.87
$AUC_{(0-T)}$ (ng.hr/ml)	166800 ± 65840	161369 ± 43491	101.23	0.8935	86.93 to 117.87

	[146998]	[161132]			
$AUC_{(0\text{-}inf)}$ (ng.hr/ml)	181055 ± 97268 [151095]	169149 ± 48146 [165363]	102.34	0.8186	86.47 to 121.13
T_{max} (hr)	26.8 ± 13.4 [26.1]	30.2 ± 16.4 [28.0]	-2.00*	0.4573#	-6.00 to 2.00#
t½ (hr)	125.42 ± 62.64 [99.83]	124.52 ± 33.87 [125.01]	n/c	0.9498	n/c

The means are arithmetic means and the CI are calculated using least square means.
* point estimate
# Non-parametric

Both formulations were well tolerated with no unexpected events and no major differences in adverse event pattern.

> ***Assessor's comment:***
> *The 90% geometric confidence intervals for the AUC and C_{max} are within the internationally acceptable range for bioequivalence of 80% to 125%.*

Pharmacokinetic conclusion

Based on the submitted bioequivalence study Bicalutamide 50 mg film-coated tablet is considered bioequivalent to Casodex 50 mg tablet.

BENEFIT RISK ASSESSMENT

Approval is recommended from the quality, preclinical and clinical point of view.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome